On the Horizon: Imaging of Vulnerable Plaques

BY BRUCE JANCIN Denver Bureau

CHICAGO — Intriguing invasive methods of identifying vulnerable coronary plaques include vaso vasorum imaging, intraarterial MRI, and several variants of optical coherence tomography, according to speakers at the annual meeting of the Society for Cardiovascular Angiography and Interventions.

► Vaso vasorum imaging. The vaso va-

sorum-the microcapillaries that form in the adventitia adjacent to atherosclerotic plaque in response to vascular injury-become more dense as inflammation due to macrophage activity increases. And this inflammation is a key factor in plaque rupture, said Dr. Stephane Carlier of Columbia University, New York.

He and his coworkers have developed an intravascular ultrasound-based technique that uses gas-filled microbubbles for contrast enhancement to assess vaso vasorum density and identify areas of intraplaque leakage or hemorrhage.

The hypothesis is that these findings will correlate with high likelihood of plaque rupture, said Dr. Carlier, who is also director of intravascular imaging and physiology at the Cardiovascular Research Foundation in New York.

► Intraarterial MRI. Conventional MRI using a big external magnet is not well suited for evaluating the composition of atheromatous plaques. Adequate resolu-

Brief summary of prescribing information	antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the activ
	metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecif
(sildenafil citrate) ubless	beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.
	Effects of VIAGRA on Other Drugs In vitro studies: Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC5
INDICATION AND USAGE	>150 µM). Given sildenafil peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely the
VIAGRA is indicated for the treatment of erectile dysfunction.	VIAGRA will after the clearance of substrates of these iscenzymes.
CONTRAINDICATIONS	In vivo studies: When VIAGRA 100 mg oral was coadministered with amlodipine, 5 mg or 10 mg oral, to hypertensiv
Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), VIAGRA wa shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organi	patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.
itrates, either regularly and/or intermittently, in any form is therefore contraindicated.	No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolize by CYP2C9.
After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered. Based on th	VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).
pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 2	VIAGRA (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum bloc
iours post dose are approximately 2 ng/mL (compared to peak plasma levels of approximately 440 ng/mL) (see CLINICA	alcohol levels of 0.08%.
PHARMACOLOGY: Pharmacokinetics and Metabolism). In the following patients: age >65, hepatic impairment (e.g. irrhosis), severe renal impairment (e.g., creatinine clearance <30 mL/min), and concomitant use of potent cytochrome P45.	In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady state pharmacokinetics of the Hi
A inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times highe	protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates. Carcinogenesis, Mutagenesis, Impairment of Fertility
han those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at pea	Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposu
oncentration, it is unknown whether nitrates can be safely coadministered at this time point.	(AUCs) for unbound sildenafil and its major metabolite of 29- and 42-times, for male and female rats, respectively, th
VIAGRA is contraindicated in patients with a known hypersensitivity to any component of the tablet.	exposúres observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenatil wa
WARNINGS	not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) (
There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore reatments for erectile dysfunction, including VIAGRA, should not be generally used in men for whom sexual activity i	10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m ² basis. Sildenafil was negative in <i>in vitro</i> bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and <i>in vitr</i>
nadvisable because of their underlying cardiovascular status.	human lymphocytes and <i>in vivo</i> mouse micronucleus assays to detect clastogenicity.
VIAGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in health	There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days t
olunteers (mean maximum decrease of 8 4/5.5 mmHg), (see CLINICAL PHARMACOLOGY: Pharmacodynamics). Whil	males, a dose producing an AUC value of more than 25 times the human male AUC.
his normally would be expected to be of little consequence in most patients, prior to prescribing VIAGRA, physicians shoul	There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers
arefully consider whether their patients with underlying cardiovascular disease could be affected adversely by suc	
asodilatory effects, especially in combination with sexual activity. Patients with the following underlying conditions can be particularly sensitive to the actions of vasodilators includin	VIAGRA is not indicated for use in newborns, children, or women. Pregnancy Category B. No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbit
/IAGRA – those with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic subaortic stenosis	which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times th
ind those with severely impaired autonomic control of blood pressure.	MRHD on a mg/m ² basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effe
There is no controlled clinical data on the safety or efficacy of VIAGRA in the following groups; if prescribed, this should	dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AU
 Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months; 	There are no adequate and well-controlled studies of sildenafil in pregnant women.
 Patients with resting hypotension (BP <90/50) or hypertension (BP >170/110); 	Geriatric Use: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil (see CLINICA PHARMACOLOGY: Pharmacokinetics in Special Populations). Since higher plasma levels may increase both the efficac
 Patients with cardiac failure or coronary artery disease causing unstable angina; 	and incidence of adverse events, a starting dose of 25 mg should be considered (see DOSAGE AND ADMINISTRATION).
• Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).	ADVERSE REACTIONS
Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have bee	PRE-MARKETING EXPERIENCE:
eported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, th vatient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage an	
ermanent loss of potency could result.	treated for longer than one year. In placebo-controlled clinical studies, the discontinuation rate due to adverse events for VIAGRA (2.5%) was no
The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations c	significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.
ildenafil (11-fold increase in AUC). If VIAGRA is prescribed to patients taking ritonavir, caution should be used. Data from	In trials of all designs, adverse events reported by patients receiving VIAGRA were generally similar. In fixed-dos
ubjects exposed to high systemic levels of sildenafil are limited. Visual disturbances occurred more commonly at highe	studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible dos
evels of sildenafil exposure. Decreased blood pressure, syncope, and prolonged erection were reported in some health rolunteers exposed to high doses of sildenafil (200-800 mg). To decrease the chance of adverse events in patients takin	studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies. When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trial
itonavir, a decrease in sildenafil dosage is recommended (see Drug Interactions, ADVERSE REACTIONS and DOSAGE ANI	the following adverse events were reported:
IDMINISTRATION).	TABLE 1. ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON
PRECAUTIONS	DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES
Seneral The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification c	Adverse Event Percentage of Patients Reporting Event
opropriate treatment following a complete medical assessment.	VIAGRA PLACEBO N=734 N=725
Before prescribing VIAGRA, it is important to note the following:	N=/34 N=/25 Headache 16% 4%
Patients on multiple antihypertensive medications were included in the pivotal clinical trials for VIAGRA. In a separate dru	Flushing 10% 1%
nteraction study, when amlodipine, 5 mg or 10 mg, and VIAGRA, 100 mg were orally administered concomitantly to	Dyspepšia 7% 2%
ypertensive patients mean additional blood pressure reduction of 8 mmHg systolic and 7 mmHg diastolic were noted (se Irug Interactions).	Nasa Congestion 4% 2%
vrug interactions). When the alpha blocker doxazosin (4 mg) and VIAGRA (25 mg) were administered simultaneously to patients with benig	Urinary Tract Infection 3% 2%
prostatic hyperplasia (BPH), mean additional reductions of supine blood pressure of 7 mmHq systolic and 7 mmHq diastoli	Abnormal Vision* 3% 0% Diarrhea 3% 1%
vere observed. When higher doses of VIAGRA and doxazosin (4 mg) were administered simultaneously, there wer	Dizziness 2% 1%
nfrequent reports of patients who experienced symptomatic postural hypotension within 1 to 4 hours of dosing	Deeb 20/ 10/
Simultaneous administration of VIAGRA to patients taking alpha blocker therapy may lead to symptomatic hypotension i come natients. Therefore: VIAGRA doses above 25 mg should not be taken within 4 bours of taking an alpha blocker	*Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these

Hash "Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision. Dut also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision. Other adverse reactions occurred at a rate of >2%, but equally common on placebo: respiratory tract infection, back pain, flu syndrome, and arthralgia. In fixed-does studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently. The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports to imprecise to be meaningful: Body as a whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury. Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart tailure, abnormal electrocardiogram, cardionyopathy.

Diordiomyopathy, constant extension extension of the providence of the providence

Metabolic and Nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, perpheral edema, hyperuncemia, yopolycemic reaction, hyperantermia. Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis. Nervous: ataxia, hypertonia, neuragia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, sonnolence, biormal dreams, reflexes decreased, hypesthesia. Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased. Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, extoliative dermatitis. Special Senses: mydrasis, conjunctivitis, photophoba, tinnitus, eye pari, dealmess, ear pain, eye hemorrhage, cataract, dry eyes. Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital dema and anorcasmia.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia. POST-MARKETING EXPERIENCE: Cardiovascular and cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular aritythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnotid and intracerebral hemorrhages, and pulmonary hemorrhage have been reported ost-marking in temporal association with the use of VIAGRA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patients underlying cardiovascular information).

Cardiovascular Disease, to a combination of brease raction, or to state the term cardiovascular information). Other events reported post-marketing to have been observed in temporal association with VIAGRA and not listed in the pre-marketing adverse reactions section above include: Mervous seizure and anxiety. Urogenitat: prolonged erection, priapism (see WARNINGS) and hematuria. Special Senses: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, paramacular edema and epistaxis. Non-arteritic anterior ischenic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDES) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing MAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hypertipidemia and smoking. It is not possible to determine whether these events are related directly to the tactors, or to other factors (see PRECAUTIONS/Information for Patients). **OVENDOSAGE** In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates were increased. In cases of overdose, standard supportive measures should be adopted as required. Renal dilaysis is not expected to

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine. Rev 10, July 2005

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tion is difficult because the coronary arteries are small, are situated deep in the thorax, and move with respiration and systolic motion of the heart.

Intraarterial MRI is a novel imaging method that sidesteps these obstacles. There is no external magnet. Magnet and coil are incorporated within the probe, which also contains radiofrequency transmission and receiver units.

Unlike conventional MRI, the intraarterial version doesn't provide pictures of the arteries in cross section; instead, it is designed specifically to analyze the lipid content within the arterial wall.

The current device is No. 6 French and deployed in a No. 8 French guiding catheter. A balloon is inflated to push the probe against an arterial plaque. Interro-

With optical coherence tomography, 'you could image a whole coronary artery in 5 or 6 seconds and get incredibly high-resolution images.'

gation of the lesion takes about 25 seconds, according to Dr. Robert L. Wilensky, a cardiologist at the University of Pennsylvania, Philadelphia. A 29-patient phase I study

has been completed. A larger phase II international trial

evaluating higher-risk patients will begin soon.

Efforts are also underway to streamline the delivery catheter from No. 8 to No. 6 French, added Dr. Wilensky, who heads the scientific advisory board for TopSpin Medical, the Israeli company developing intraarterial MRI.

► Optical coherence tomography. This extremely high-resolution broadband light-based imaging method provides tremendous structural detail.

With a theoretic resolution of 5-7 micrometers and somewhat less in actual practice, optical coherence tomography (OCT) is well-suited for in-depth morphologic evaluation of thin-capped fibroatheromas, the plaque type believed to be at greatest risk of rupture and resultant MI, said Dr. Gregg W. Stone, professor of medicine at Columbia University and vice chairman of the Cardiovascular Research Foundation.

There is a daunting obstacle to commercial development of OCT, however: At present, the intravascular probe requires arterial occlusion, as do OCT's variants, including optical frequency domain imaging and polarization-sensitive OCT.

Optical frequency domain imaging "is basically OCT on steroids," according to Dr. Stone. "It allows much, much faster acquisition rates.

"In fact, you can pull back at up to 12 mm/second, so you could image a whole coronary artery in 5 or 6 seconds and get incredibly high-resolution images," he added.

Polarization-sensitive OCT takes advantage of the birefringence of collagen fibers, enabling physicians to readily separate collagen from noncollagen tissues.

Household in Sincerane Careford and the second seco ritonavir's marked effects on a broad range of P450 substrates. VIAGRA had no effect on ritonavir pharmacokinetics (see DOSAGE AND ADMINISTRATION). Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels. It can be expected that concomitant administration of CYP3A4 inducers, such as ritampin, will decrease plasma levels of sildenafil.

sildenafil. Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of VIAGRA. Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 nhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic

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