

APPENDIX A-1

NOT FOR PUBLICATION

UNITED STATES COURT OF APPEALS

FOR THE NINTH CIRCUIT

FILED

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MOLLY C. DWYER, CLERK
U.S. COURT OF APPEALS

DAVID JAY DEARINGER Sr.; GANNA
P. DEARINGER,

Plaintiffs - Appellants,

v.

ELI LILLY AND COMPANY, a
corporation,

Defendant - Appellee.

No. 24-682

D.C. No.

2:21-cv-00060-JCC

MEMORANDUM*

Appeal from the United States District Court
for the Western District of Washington
John C. Coughenour, District Judge, Presiding

Argued and Submitted February 13, 2026
Seattle, Washington

Before: PAEZ and BUMATAY, Circuit Judges, and KASUBHAI, District Judge.**

Plaintiffs David Dearing (Dearing) and his wife Ganna Dearing appeal
the district court's grant of summary judgment to defendant Eli Lilly and Company

* This disposition is not appropriate for publication and is not precedent
except as provided by Ninth Circuit Rule 36-3.

** The Honorable Mustafa T. Kasubhai, United States District Judge for
the District of Oregon, sitting by designation.

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(Lilly). In January 2018, Dearinger suffered an intracerebral hemorrhage (ICH), a type of stroke, after taking Cialis, a prescription medication manufactured by Lilly. The Dearingers allege that Lilly's failure to warn adequately Dearinger's physicians of the risk of ICH from the use of Cialis caused his ICH.

We review de novo the district court's grant of summary judgment. *See Vasquez v. Cnty. of Los Angeles*, 349 F.3d 634, 639 (9th Cir. 2003). We have jurisdiction pursuant to 28 U.S.C. § 1291. We affirm.

1. ***Appointment of counsel.*** Assuming *arguendo* that the district court abused its discretion in denying the Dearingers' two motions for appointment of counsel, we conclude, for the reasons discussed below, that any such error was harmless. As we explain, summary judgment was appropriately granted to Lilly based on the deposition testimony of Dr. Bardin and Dearinger.

2. ***Proximate causation.*** The Washington Products Liability Act, Wash. Rev. Code § 7.72.010 *et seq.*, requires that a plaintiff establish proximate cause, composed of both cause in fact and legal causation. *Hiner v. Bridgestone/Firestone, Inc.*, 978 P.2d 505, 509 (Wash. 1999). "Cause in fact refers to the 'but for' consequences of an act[.]" *Hartley v. State*, 698 P.2d 77, 83 (Wash. 1985). "In the context of prescription drugs, the learned intermediary doctrine provides 'the manufacturer satisfies its duty to warn the patient of the risks of its product where it properly warns the prescribing physician.'" *Dearinger v. Eli Lilly*

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& Co., 510 P.3d 326, 329 (Wash. 2022) (citation omitted). “In other words, ‘[t]he manufacturer’s duty to provide warnings to patients transfers to the doctor, who is in a better position to communicate them to the patient.’” *Id.* (citation omitted).

To establish proximate cause for a claim that a manufacturer defectively designed its labels or failed to warn consumers of risks, a plaintiff must therefore demonstrate that: if the prescribing physician “had [] been adequately warned of the risks, [he or she] would have treated the product differently and avoided the harm.” *Ayers v. Johnson & Johnson Baby Prods. Co.*, 797 P.2d 527, 530 (Wash. App. 1990), *aff’d*, 818 P.2d 1337 (Wash. 1991)..

Here, the district court concluded that the Dearingers’ defective design and failure-to-warn claims under the WPLA could not survive summary judgment because the Dearingers failed to establish proximate cause. We agree.

In so concluding, we rely on the following undisputed facts. In 2007, Dearinger’s urologist, Dr. Bardin, prescribed him 20mg doses of Cialis, to take on an as-needed basis. In 2015, Dr. Bardin modified the prescription to a daily 5mg dose. By March 2017, Dearinger was no longer seeing Dr. Bardin. At that time, Dr. Horst, Dearinger’s primary care physician, prescribed a refill of the daily 5mg dose. Dr. Horst never prescribed any 20mg pills to Dearinger. We consider the significance of these facts below.

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A. **Dr. Bardin.** Dr. Bardin testified at his deposition that, given an alternative warning label, he would not have changed his decision to prescribe Cialis to Dearing. Because it is undisputed that Dr. Bardin would not have “treated the product differently and avoided the harm,” the Dearingers fail to establish that Lilly’s then-existing warning label proximately caused Dearing’s ICH. *See Ayers*, 797 P.2d at 530.

B. **Dr. Horst.** Dr. Horst testified at his deposition that, given an alternative warning label, he would not have prescribed Cialis to someone with Dearing’s “family history” of ICH, and would have “hesitated” to prescribe Cialis to Dearing. This theory of proximate causation is foreclosed, however, by Dearing’s testimony regarding his use of Cialis. Dr. Horst only prescribed Dearing 5mg pills, and Dearing testified that he stopped taking these pills “shortly after” he was prescribed them in March 2017. The Dearingers argue that Dr. Horst’s testimony could still be relevant if the court were to consider Dr. Horst’s role as a treating physician during the period in which Dr. Bardin was prescribing the 20mg pills.

The Washington Supreme Court has not yet addressed whether a drug manufacturer’s duty to warn extends to a patient’s treating physicians. “In the absence of such a decision, [we] must predict how the [Washington Supreme Court] would decide the issue using intermediate appellate court decisions,

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decisions from other jurisdictions, statutes, treatises, and restatements as guidance.” *See In re Kirkland*, 915 F.2d 1236, 1239 (9th Cir. 1990). The Washington Court of Appeals has addressed this issue in an unpublished opinion, but declined to expand the doctrine. *See Falsberg v. GlaxoSmithKline, PLC*, 2013 WL 4822205, at *4 (Wash. App. Sept. 9, 2013). While *Falsberg* is “certainly not dispositive of how the [Washington] Supreme Court would rule,” we may consider it as persuasive authority. *See Emps. Ins. of Wausau v. Granite State Ins. Co.*, 330 F.3d 1214, 1220 n.8 (9th Cir. 2003). Given the Washington Supreme Court’s focus on the “unique” role of prescribing physicians in this context, as described in *Falsberg*, we are not persuaded that it would extend a drug manufacturer’s duty to warn to treating physicians, and we decline to apply such a rule here. *See Falsberg*, 2013 WL 4822205, at *4.

3. ***Sham affidavit rule.*** Assuming *arguendo* that the district court abused its discretion in relying on the sham affidavit rule to deny the Dearingers’ motion for reconsideration, we conclude that any such error was harmless. This is because, even considering Dearinger’s sworn statement that Dr. Horst was “the actual prescriber” of the Cialis at issue, Lilly was entitled to summary judgment on the merits, as discussed above.

4. ***Omission of obvious defendants.*** The district court did not err by failing to advise the Dearingers, as pro se litigants, to seek leave to amend their

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complaint to assert claims against Dearinger's physicians. The physicians were not "obvious[ly]" omitted defendants because the Dearingers never made allegations of wrongdoing against them in their complaint, even construing it liberally. *See Wilborn v. Escalderon*, 789 F.2d 1328, 1332 (9th Cir. 1986).

AFFIRMED.

Appendix E-1

THE HONORABLE JOHN C. COUGHENOUR

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

DAVID DEARINGER and GANNA
DEARINGER,

Plaintiffs,

v.

ELI LILLY AND COMPANY ,

Defendant.

CASE NO. C21-0060-JCC

ORDER

This matter comes before the Court on Defendant Eli Lilly and Company's second motion for summary judgment (Dkt. No. 86) and Plaintiffs' motion for reconsideration (Dkt. No. 87). Having thoroughly considered the briefing and the relevant record, and finding oral argument unnecessary, the Court hereby GRANTS Defendant's motion (Dkt. No. 86), DENIES Plaintiffs' motion (Dkt. No. 87), and DISMISSES Plaintiffs' Second Amended Complaint ("SAC") (Dkt. No. 37) with prejudice for the reasons explained below.

I. BACKGROUND

In 2018, Plaintiff David Dearing suffered an intracranial brain hemorrhage, *i.e.*, a stroke, resulting in the permanent loss of "sensory and motor function of the left side of his body." (Dkt. No. 37 at 2-3.) The SAC states that Defendant's prescription erectile dysfunction

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1 drug Cialis was the cause. (*Id.*) Accordingly, it asserts Washington's Product Liability Act
2 ("WPLA") claims, along with fraudulent concealment and loss of consortium. (*See generally id.*)

3 On December 18, 2023, the Court granted in part Defendant's motion for summary
4 judgment, dismissing Plaintiffs' failure-to-warn claim (Counts 2 and 3) and fraudulent
5 concealment claim (Count 4). (Dkt. No. 84.) However, summary judgment was denied on
6 Plaintiffs WPLA design defect claim (Count 1) and loss of consortium claim (Count 5). (*Id.*)
7 Defendant now moves for summary judgment on those claims. (Dkt. No. 86.) Separately,
8 Plaintiff moves to amend the Court's order (Dkt. No. 84) dismissing the failure to warn and
9 fraudulent concealment claims. (Dkt. No. 87.)

10 II. DISCUSSION

11 A. Motion for Summary Judgment

12 "The court shall grant summary judgment if the movant shows that there is no genuine
13 dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R.
14 Civ. P. 56(a). In making such a determination, the Court must view the facts in the light most
15 favorable to the nonmoving party and draw justifiable inferences in that party's favor. *Anderson*
16 *v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986). Ultimately, summary judgment is appropriate
17 against a party who "fails to make a showing sufficient to establish the existence of an element
18 essential to that party's case, and on which that party will bear the burden of proof at trial."
19 *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986).

20 B. Federal Preemption

21 Defendant argues that Plaintiffs' design defect claim is preempted because federal law
22 forbids Defendant from changing Cialis's label design without prior Food and Drug
23 Administration ("FDA") approval. (Dkt. No. 86 at 12.) FDA regulations provide that once a
24 drug, whether generic or brand-name, is approved, the manufacturer is prohibited from making
25 any major changes to the "qualitative or quantitative formulation of the drug product, including
26 inactive ingredients, or in the specifications provided in the approved application." 21 C.F.R.

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1 § 314.70(b)(2)(i).¹ Federal regulation defines three classes of changes: “major changes,”
2 “moderate changes,” and “minor changes.” 21 C.F.R. § 314.70(b)–(d). Major changes “include,
3 but are not limited to[,] . . . changes in the qualitative or quantitative *formulation* of the drug
4 product.” *Id.* § 314.70(b)(2)(i) (emphasis added.)

5 Here, it is uncontroverted that Cialis is an FDA-approved prescription medication which,
6 under federal law, Defendant is prohibited from altering its formulation without prior FDA
7 approval. Based on the plain meaning of the regulation, Defendant could not alter the medication
8 without submission to the FDA for “approval *prior* to distribution of the product made using the
9 change.” *See id.* (emphasis added). Consequently, to the extent Plaintiffs’ design defect claim is
10 based on Cialis’s formulation, it is preempted. *See Yates v. Ortho-McNeil Pharm., Inc.*, 808 F.3d
11 281, 296–300 (6th Cir. 2015) (“[T]o the extent Yates argues that defendants should have altered
12 the formulation of ORTHO EVRA® after the FDA had approved the patch, we find this claim
13 clearly preempted.”) Accordingly, all that remains of Plaintiffs’ defective design claim is a claim
14 sounding in defective *labeling*.

15 **C. Defective Labeling under the WPLA**

16 Defendant now seeks summary judgment on the remainder of Plaintiffs’ WPLA claim for
17 defective labeling, arguing that, without any evidence supporting proximate cause, the claim fails
18 as a matter of law. (*See* Dkt. No. 86 at 6–18.)²

19 Under Washington law, “[i]n a products liability suit alleging inadequate warnings, the
20 plaintiff must show that his or her injury was *proximately caused* by a product that was not

21 ¹ Moderate changes must be reported to the FDA “at least 30 days *prior* to distribution of
22 the drug product made using the change.” *Id.* § 314.70(c) (emphasis added). Minor changes need
23 only be reported in an annual report to the FDA. *Id.* § 314.70(d)(3). Major changes require
FDA’s “approval prior to distribution of the product made using the change.” *Id.* § 314.70(b).

24 ² Defendant also argues that Plaintiffs’ design defect claim is barred under comment k to
25 section 402A of the Restatement (Second) of Torts. (*Id.* at 14–15.) But that is not so. By the
comment’s express terms, proper preparation, marketing, and warnings are *prerequisites* to a
26 manufacturer being able to qualify for immunity from strict liability. *See Taylor v. Intuitive
Surgical, Inc.*, 389 P.3d 517, 528 (2017).

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1 reasonably safe because adequate warnings or instructions were not provided.” *Ayers By &*
2 *Through Ayers v. Johnson & Johnson Baby Prod. Co., a Subsidiary of Johnson & Johnson Co.*,
3 818 P.2d 1337, 1339 (1991) (emphasis added) (citations omitted). To establish proximate
4 causation, the plaintiff must show both cause in fact and legal causation. *Id.* (citation omitted).
5 “Cause in fact refers to the actual connection between the act and an injury—but for the act, the
6 injury would not have occurred.” *Sherman v. Pfizer, Inc.*, 8 Wash. App.2d 686, 687 (2019). A
7 warnings-based design defect claim requires proof that a different warning would have caused a
8 different outcome. *See Rodman v. Ethicon, Inc.*, 2021 WL 2434521, slip op. at 5 (W.D. Wash.
9 2021) (proximate cause requires proof that a different warning would have “avoided the harm.”).

10 According to Plaintiffs, the Cialis dose at issue was, in fact, prescribed by Dr. Bardin.
11 (Dkt. Nos. 60-5 at 6–7, 60-7 at 8.) And Dr. Bardin testified that (a) he was aware of Cialis’s risk
12 of hemorrhagic strokes and (b) even if he had received a stronger warning of the risk(s), such as
13 the one which Plaintiffs later suggest is adequate, Dr. Bardin would not have “changed [his]
14 decision to prescribe Cialis [to Mr. Dearing].” (Dkt. Nos. 60-1 at 17, 26, 27, 60-7 at 15.)
15 Plaintiffs fail to provide any evidence rebutting this testimony.

16 Accordingly, the Court finds that Plaintiffs fail to establish a genuine issue of fact on the
17 issue of proximate cause. And without this, Plaintiffs cannot proceed to trial on these claims.
18 Accordingly, summary judgment is GRANTED.

19 **D. Loss of Consortium**

20 As Plaintiffs’ predicate causes of action are dismissed, their loss-of-consortium claim *a*
21 *fortiori* fails, because such claims cannot independently stand. *See Carter v. Ethicon Inc.*, 2021
22 WL 1893749, slip op. at 3 (W.D. Wash. 2021) (dismissing loss-of-consortium claim because all
23 of plaintiff’s statutory claims were dismissed).

24 Accordingly, Plaintiffs’ loss of consortium claim is DISMISSED.
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E. Motion for Reconsideration

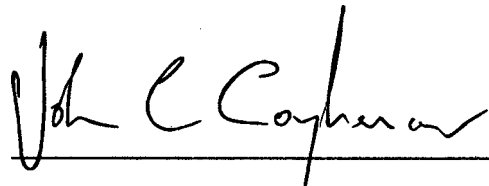
Plaintiffs' motion for reconsideration (Dkt. No. 87) is premised on a *new* factual allegation that Dr. Horst was "the actual prescriber" of the Cialis, not Dr. Bardin. (*Id.* at 2-7.) But this flies in the face of Plaintiffs' earlier sworn testimony to the contrary. (Dkt. Nos. 60-5 at 6-7, 60-7 at 8) (stating that Dr. Bardin prescribed the Cialis). "A party cannot create an issue of fact by an affidavit contradicting his prior deposition testimony." *Kennedy v. Allied Mut. Ins. Co.*, 952 F.2d 262, 266 (9th Cir. 1991). Accordingly, the Court will not permit contradictory testimony from creating an issue of fact sufficient to survive summary judgment. *Russell v. Pac. Motor Trucking Co.*, 672 F. App'x 629, 630 (9th Cir. 2016) ("The district court did not abuse its discretion in disregarding those portions of the affidavit that directly contradicted [plaintiff's] former deposition testimony.")

Plaintiffs' motion for reconsideration (Dkt. No. 87) is therefore DENIED.

III. CONCLUSION

For the foregoing reasons, Defendant's motion for summary judgment (Dkt. No. 86) is GRANTED and Plaintiffs' motion for reconsideration (Dkt. No. 87) is DENIED. The Court DISMISSES Plaintiffs' complaint (Dkt. No. 37) with prejudice.

DATED this 5th day of February 2024.



John C. Coughenour
UNITED STATES DISTRICT JUDGE

EFFECTS OF SILDENAFIL ON THE RELAXATION OF HUMAN CORPUS CAVERNOSUM TISSUE IN VITRO AND ON THE ACTIVITIES OF CYCLIC NUCLEOTIDE PHOSPHODIESTERASE ISOZYMES

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ABSTRACT

Purpose: Sildenafil, an inhibitor of cGMP-specific phosphodiesterase 5 (PDE5), is currently undergoing evaluation as an oral therapy for penile erectile dysfunction. The aims of this study were to investigate the mechanism of action of sildenafil on the neurogenic relaxation of human corpus cavernosum (HCC) in vitro and to determine the activity of sildenafil against a full range of PDE isozymes.

Materials and Methods: Strips of HCC tissue were precontracted with phenylephrine. Relaxation responses resulting from electrical field stimulation (EFS) were then determined in the presence and absence of sildenafil. The effects of sildenafil on PDE1 to 5 prepared from human tissues and PDE6 from bovine retina were determined by measuring the conversion of [³H]-cGMP or [³H]-cAMP to their respective [³H]-5'-mononucleotides.

Results: Sildenafil (0.001 to 1 μ M) enhanced the EFS-induced, nitric oxide (NO) dependent, relaxation of HCC in a concentration-dependent manner to a maximum of 3 times the pretreatment level at 1 μ M sildenafil. Compared with zaprinast, an early PDE5 inhibitor, sildenafil was approximately 240-fold more potent, inhibiting PDE5 from HCC with a geometric mean IC₅₀ of 3.5 nM. For sildenafil, IC₅₀ values for inhibition of PDE1 to 4 were 80 to more than 8500 times greater than that for PDE5 and the IC₅₀ for PDE6 (33 nM) was approximately 9-fold greater.

Conclusions: The data support the proposal that enhancement of penile erection by sildenafil in patients with erectile dysfunction involves potentiation of the NO-stimulated cGMP signal mediating relaxation of cavernosal smooth muscle during sexual stimulation. Sildenafil is a potent inhibitor of PDE5 from HCC, with high selectivity for PDE5 relative to other PDE isozymes.

KEY WORDS: impotence, phosphodiesterase inhibitors, nitric oxide, penile erection, guanylate cyclase

Penile erection is a hemodynamic process involving relaxation of smooth muscle of the corpus cavernosum and its associated arterioles. This relaxation process results in an increased flow of blood into the trabecular spaces of the corpora cavernosa.^{1,2} Smooth muscle relaxation is mediated by nitric oxide (NO) which, during sexual stimulation, is synthesized in the nerve terminals of parasympathetic non-adrenergic, non-cholinergic (NANC) neurons in the penis and also by the endothelial cells lining blood vessels and the lacunar spaces of the corpora cavernosa.³⁻⁵ Although the effector system has yet to be fully defined, NO activates guanylate cyclase resulting in an increased conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP provides the signal which leads to relaxation of smooth muscle of the corpus cavernosum and penile arterioles.⁵ The level of cGMP is regulated by a balance between the rate of synthesis by guanylate cyclase and the rate of hydrolytic breakdown to guanosine 5'-monophosphate (GMP) by cyclic nucleotide phosphodiesterase (PDE) isozymes.⁶ Therefore, agents that inhibit cGMP hydrolysis may increase the cGMP signal and could be expected to enhance relaxation of smooth muscle in the corpus cavernosum and thereby facilitate penile erectile responses. This proposal is supported by reports that zaprinast (fig. 1), an inhibitor of cGMP-specific PDE5, enhanced the NO-

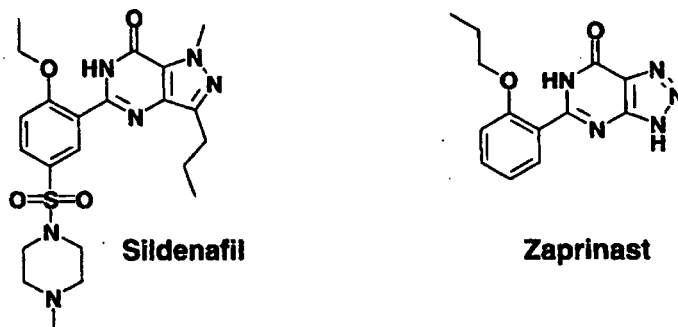


FIG. 1. Structures of sildenafil and zaprinast

dependent relaxation of human and rabbit corpus cavernosal tissue in vitro^{7,8} and, when administered by intracavernosal (i.c.) injection to dogs and monkeys, augmented penile tumescence produced by pelvic nerve stimulation and i.c. sodium nitroprusside, respectively.^{9,10}

Of the PDE isozyme families, only PDE5 and PDE6 are specific for cGMP as a substrate. PDE3 and PDE4 are specific for cyclic adenosine monophosphate (cAMP), and PDE1 and PDE2 hydrolyse both cGMP and cAMP.¹¹ Sildenafil (UK-92480; fig. 1) is a potent inhibitor of the cGMP-specific PDE5 found in human corpus cavernosum (HCC). It effectively blocks PDE5-mediated hydrolysis of cGMP and has a re-

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ported IC_{50} of 3.9 nM.¹² Furthermore, sildenafil has been shown to elevate the level of cGMP, but not cAMP, in rabbit corpus cavernosal tissue *in vitro*.¹³ It has also been shown to be effective in increasing the frequency and duration of erections both in men with organic erectile dysfunction¹⁴ and those in whom no organic cause could be established for the dysfunction.^{12,15} Sildenafil is now under development as a novel, orally active agent for the treatment of penile erectile dysfunction.

Here, the mechanism of action of sildenafil has been further investigated by determining its effects on the relaxation of HCC tissue induced by electrical field stimulation (EFS). An inhibitor of soluble guanylate cyclase, 1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ),¹⁶ was used as a comparator to fully define the role of cGMP in NO-dependent relaxation of HCC tissue. In addition, sildenafil's kinetic mode of inhibition of human PDE5 has been determined, and its PDE selectivity profile has been fully defined by determining its activity as an inhibitor of PDE1 to 6. The PDE5 inhibitor, zaprinast,¹⁷ was included in this latter study for comparison.

MATERIALS AND METHODS

Source of HCC tissue and tissue preparation for EFS-induced relaxation. This work was approved by the Medical Research Ethics Committee of Bristol Southmead Hospital and by the South Eastern Medical Ethics Committee.

The samples of corpus cavernosal tissue used to study the functional effects of sildenafil were obtained from nine men with erectile dysfunction (range 47 to 69 years of age) undergoing surgery for implantation of penile prostheses, the removal of this tissue being a normal part of the operation. Fresh tissue was collected into oxygenated, ice-cold modified Krebs buffer (NaCl, 118 mM; NaHCO₃, 25 mM; KCl, 4 mM; NaH₂PO₄, 0.5 mM; CaCl₂, 0.7 mM) and used for functional experiments within 24 hours of collection. Previous work with rabbit corpus cavernosal tissue showed that samples stored under these conditions maintained mechanical responses to EFS similar to those observed with freshly dissected tissues.

Strips of HCC (approximately 5 mm. x 2 mm.) were tied at each end with cotton threads and mounted in 15 ml. capacity organ chambers containing Krebs-bicarbonate solution (NaCl, 118 mM; NaHCO₃, 25 mM; KCl, 4.7 mM; KH₂PO₄, 1.2 mM; MgSO₄, 1.2 mM; glucose, 11 mM; CaCl₂, 1.5 mM) maintained at 37°C and continuously aerated with 95% O₂ and 5% CO₂. The upper end of each strip was suspended from an isometric force transducer which was in turn linked to an amplifier and chart recorder. The initial resting tension of each strip was set at 2 gm. and the tissues were allowed to equilibrate for 1.5 hours. The tissue samples were then washed with 120 mM KCl in Krebs-bicarbonate solution for 5 minutes to depolarize the tissue and induce a contractile response. Depolarization with KCl increases and stabilizes subsequent submaximal contractile responses to phenylephrine.⁷ Following this step, the tissues were allowed to return to baseline tension by repeatedly washing for 30 minutes with Krebs solution modified to contain 1 μ M atropine and 5 μ M guanethidine to block muscarinic receptors and prevent the release of norepinephrine, respectively, during subsequent EFS stimulation. This modified Krebs solution was used throughout subsequent experiments.

Effects of sildenafil on EFS-induced relaxation of HCC tissue. Each tissue strip was submaximally contracted to approximately 70% of the KCl-induced contraction by adding phenylephrine hydrochloride to each organ chamber to a final concentration of 10 μ M. After the phenylephrine contractile responses had stabilized (10 minutes), the tissues were subjected to EFS-induced relaxation at 10 volts (0.8 msec. pulse duration) using sequential frequencies of 1, 2, 4,

8, 16 and, in some experiments, 32 Hz delivered as 10-second trains at 2 minutes intervals. Any tissues that failed to show at least 6% relaxation to EFS at 16 Hz were discarded.

HCC tissue strips were washed, the organ baths were refilled with 15 ml. of Krebs buffer and then either 50 μ L of sildenafil solution in 0.6% v/v lactic acid vehicle or 50 μ L of vehicle (time-matched control) was added. The final concentration of sildenafil used in these studies ranged from 1 nM to 1 μ M. The tissues were allowed to equilibrate with sildenafil or vehicle for 15 minutes and then reset to the original baseline tension before again being contracted with phenylephrine. After the contractile responses stabilized, the tissues were subjected to sequential-frequency EFS as described above. The tissues were washed for 15 minutes before adding vehicle or the next concentration of sildenafil and repeating the EFS profile. The time-matched control tissues were monitored to ensure that the EFS response was stable over the course of the experiments, and to verify that any changes observed in the EFS response after exposure to sildenafil were drug effects.

Characterization of EFS-induced relaxation of HCC tissue. Tissue strips were contracted with 10 μ M phenylephrine and a pretreatment EFS frequency response profile was generated as described above. Tetrodotoxin (1 μ M), the NO-synthase inhibitor N^ω-nitro-L-arginine (L-NOArg; 10 or 30 μ M), or the guanylate cyclase inhibitor 1*H*-1, 2, 4 oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ; 300 nM or 3 μ M) were then added. After a 5-minute equilibration period, a second EFS frequency response curve was generated. The specificity of L-NOArg (10 μ M) inhibition of EFS-induced relaxation was evaluated by determining its reversibility with L-arginine (300 μ M) and the reversibility of ODQ-induced suppression of relaxation by repeated washing of the tissues.

Statistical analysis for EFS experiments. Response to treatment with sildenafil was assessed by determining the level of tissue relaxation at 1-16 Hz and the duration of the response at 8 Hz. The tissue relaxation responses induced by EFS at each frequency were expressed as a percentage of the phenylephrine-induced contractile response. Parallel cubic regressions were then calculated from plots of the percent relaxation versus the log of the EFS frequency for each concentration of sildenafil and for the corresponding time-matched control. The calculated percent relaxation values where the cubic regression curve crossed the 2-Hz line (arbitrarily selected and designated as the "fitted value at 2 Hz") were recorded and used for subsequent analysis. Because there was a difference between the pretreatment means for the sildenafil and time-matched control groups, an overall analysis of covariance was carried out which compared the sildenafil-treated tissues and time-matched controls directly, after adjustment for pretreatment values.

The duration of relaxation resulting from a 10-second stimulation at 8 Hz was assessed by measuring the width of the relaxation response profile at half maximal relaxation and expressing the value in seconds. Student's unpaired *t* tests were used to determine the significance of differences between the sildenafil-treated group and the time-matched control group.

Preparation of soluble fractions from human tissues and bovine retinas. Frozen HCC tissue, human cardiac ventricle and human *gluteus maximus* skeletal muscle were obtained from ILM (Exton, Pennsylvania). Tissue homogenates were prepared from these as previously described.¹² Platelet-rich plasma (PRP) was obtained by centrifuging fresh human blood at 360 g for 10 minutes. The PRP was then centrifuged at 1400 g for 10 minutes to sediment the platelets. Platelets were resuspended in 1 ml. ice-cold homogenization buffer (20 mM HEPES containing 0.25 M sucrose, 1 mM EDTA, 1 mM phenylmethyl sulfonylfluoride [PMSF], pH 7.2) for every 10 ml. of blood and disrupted by sonication (Kontes Microultrasonic Cell Disrupter, Burkard Scientific, Uxbridge, Mid-

dlex, UK). Bovine eyes were obtained fresh from the local abattoir. Retinas were dissected free and homogenized in the homogenization buffer described above (approximately 2 ml. per retina) using a Polytron PT 1200B homogenizer (Kematica AG, Lucerne, Sweden) at high setting (3×10 -second bursts). The retinal homogenate was filtered through two layers of surgical gauze to remove undispersed tissue and fibrous material. The homogenates of all tissues were then centrifuged at 100,000 g for 60 minutes at 4°C. The supernatants were recovered and filtered through a 0.2 μ m. filter and either used directly for preparation of PDE isozymes or stored in liquid nitrogen prior to use.

Isolation of phosphodiesterase isozymes. PDE activities in the soluble fractions prepared from tissues were separated using a Pharmacia FPLC system (Pharmacia Ltd, Milton Keynes, UK) with a Mono Q anion exchange column (1 ml. bed volume, Pharmacia Ltd). The Mono Q column was pre-equilibrated with 20 mM HEPES buffer (pH 7.2) containing 1 mM EDTA and 0.5 mM PMSF followed by application of a 2- to 5-ml. sample of tissue soluble fraction. The column was then washed with 5 ml. of buffer. The PDE isozymes were eluted using a continuous gradient of 0 to 500 mM NaCl in the same buffer (55-ml. total volume) at a flow rate of 1 ml. per minute, and 2-ml. fractions were collected. cAMP and cGMP PDE activities in the column fractions were determined as described below and PDE1 to 5 activities were characterized as previously described.¹² PDE2, 3 and 5 were isolated from the cytosol prepared from HCC, PDE1 from cardiac ventricle and PDE4 from skeletal muscle. The identity of PDE6 isolated from the bovine retina cytosol was confirmed through its monospecificity for cGMP as substrate and its activation (8 to 9 fold) by trypsin. The column fractions showing the highest level of each characterized PDE activity were pooled and stored at -80°C until used in inhibition experiments.

Determination of phosphodiesterase activity. The cyclic nucleotide PDE activity in FPLC fractions was determined using a modification of the two-step radioisotopic procedure of Thompson and Appleman.¹⁸ The reaction mixture (100 μ L total volume) contained column fraction eluate (10 to 25 μ L), [^{3} H]-cGMP (0.5 μ M, 2 μ Ci/ml.) or [^{3} H]-cAMP (0.5 μ M, 2 μ Ci/ml.), bovine serum albumin (0.5 mg/ml.), and MgCl_2 (5 mM) in Tris.HCl buffer (15 mM, pH 7.4). Reactions were initiated by the addition of the radiolabeled substrate and the samples incubated in a water bath at 30°C for 30 minutes. The reaction was stopped by immersing the sample tubes in boiling water for 2 minutes. The 5'-mononucleotides formed by hydrolysis of cyclic nucleotides were determined after their further conversion to nucleosides using snake venom (*Ophiophagus hannah*) nucleotidase activity as described by Thompson and Appelmann.¹⁸

For studies of the inhibition of PDE isozyme activities, sildenafil and zaprinast were added to incubation mixtures in dimethyl sulfoxide (DMSO; final concentration 2%, v/v) and the reaction was initiated by addition of the PDE enzyme fraction. All inhibition experiments were conducted under conditions where the level of cGMP or cAMP hydrolysis did not exceed 15%, and product formation increased linearly with time and amount of enzyme. [^{3} H]-cGMP was used as the substrate for PDE1, 2, 5 and 6, and [^{3} H]-cAMP as substrate for PDE 3 and 4.

In studies of the kinetics of inhibition of PDE5 by sildenafil, [^{3} H]-cGMP substrate concentrations ranged from 0.5 μ M to 10 μ M and initial rates of hydrolysis were determined in the absence of sildenafil and in the presence of 4, 8, 20 and 40 nM sildenafil.

Data analysis for enzyme inhibition studies. IC_{50} values for inhibition of PDE6 were determined from sigmoidal curves, fitted to plots of enzyme activity versus log compound concentration using a curve fitting program.¹⁹ In PDE5 kinetics data were analyzed using Lineweaver-

Burk plots and Dixon plots with velocities weighted according to the assumption of similar variance. The K_m for PDE5, the mode of inhibition of PDE5 by sildenafil, and the K_i for sildenafil were determined from these analyses.

Materials. Sildenafil was synthesised by Pfizer Ltd., Sandwich, UK. ODQ was purchased from Tocris Cookson Ltd., Bristol, U.K. All other chemicals were obtained from Sigma-Aldrich Chemical Company Ltd., Poole, UK.

RESULTS

Characterization of EFS-induced relaxation of HCC tissue. The majority of HCC tissue samples obtained showed contractile responses upon addition of phenylephrine. However, only 56% of the samples (obtained from 5 of the 9 men) exhibited subsequent relaxation responses to EFS at 16 Hz that exceeded 6% of the phenylephrine-induced tone, and only these tissues were used in subsequent experiments. In the tissues that responded, EFS elicited transient, frequency-dependent relaxation responses which increased in magnitude over the range of 2 to 16 Hz (fig. 2). Relaxation responses were completely inhibited by 1 μ M tetrodotoxin and also by 30 μ M L-NOArg (data not shown). At a lower concentration of L-NOArg (10 μ M), relaxation responses were reduced by approximately 89% and this inhibition was partially reversed by addition of 300 μ M L-arginine, but not D-arginine (fig. 2). ODQ (300 nM), a guanylate cyclase inhibitor, inhibited relaxation responses induced by EFS at 16 Hz, by a mean of 63% and produced 95% inhibition at 3 μ M (fig. 3). This inhibition was partially reversed by repeatedly washing the tissues for 45 minutes (data not shown).

Effects of sildenafil on EFS-induced relaxation of HCC tissue. When HCC tissues were not subjected to EFS, sildenafil had little or no effect on the phenylephrine-induced contraction: even at the highest concentration tested (1000 nM), sildenafil diminished phenylephrine-induced contraction of HCC tissues by less than 13%, which was not statistically significant (fig. 4). However, during EFS, sildenafil (1 to 1000 nM) enhanced the EFS-induced relaxation responses of HCC tissue strips in a concentration-dependent manner (fig. 5). The increases observed at 10, 100 and 1000 nM sildenafil were statistically significant over the 1 to 16 Hz EFS range when compared with the relaxation responses observed for time-matched control tissues. The effects of sildenafil were proportionally greater at low stimulation frequencies (1 to 2 Hz), where the mean relaxation response in the presence of 1000 nM sildenafil was increased to a maximum of 3 times the pretreatment level.

In addition to enhancing the magnitude of HCC tissue relaxation during EFS, sildenafil also increased the duration of the relaxation responses (fig. 6 and fig. 7). This effect was quantified by determining the width of the relaxation response profile at half maximal relaxation (fig. 6). Under control conditions, the duration of relaxation was relatively independent of the magnitude of relaxation; while the mean relaxation response for 14 tissues increased by 42% between stimulation frequencies of 4 Hz and 16 Hz, the mean duration of response increased by less than 14% over the same frequency range. The duration of responses, determined at 8 Hz, for tissues treated with 100 nM and 1000 nM sildenafil were 53% and 100% greater, respectively, than the corresponding values for control tissues (fig. 7).

Effects of sildenafil and zaprinast on PDE isozymes. Sildenafil was a potent inhibitor of PDE5 isolated from HCC, with a geometric mean IC_{50} of 3.5 nM (table 1). Sildenafil was approximately 240-fold more potent than zaprinast (IC_{50} = 856 nM). Sildenafil and zaprinast both had low potency against PDE2 and PDE3, the other phosphodiesterases found in HCC, and were also weak inhibitors of PDE4 (IC_{50} values $\geq$ 7680 nM and $\geq$ 77,400 nM respectively). Sildenafil had moderate activity against PDE1 from human cardiac ventri-

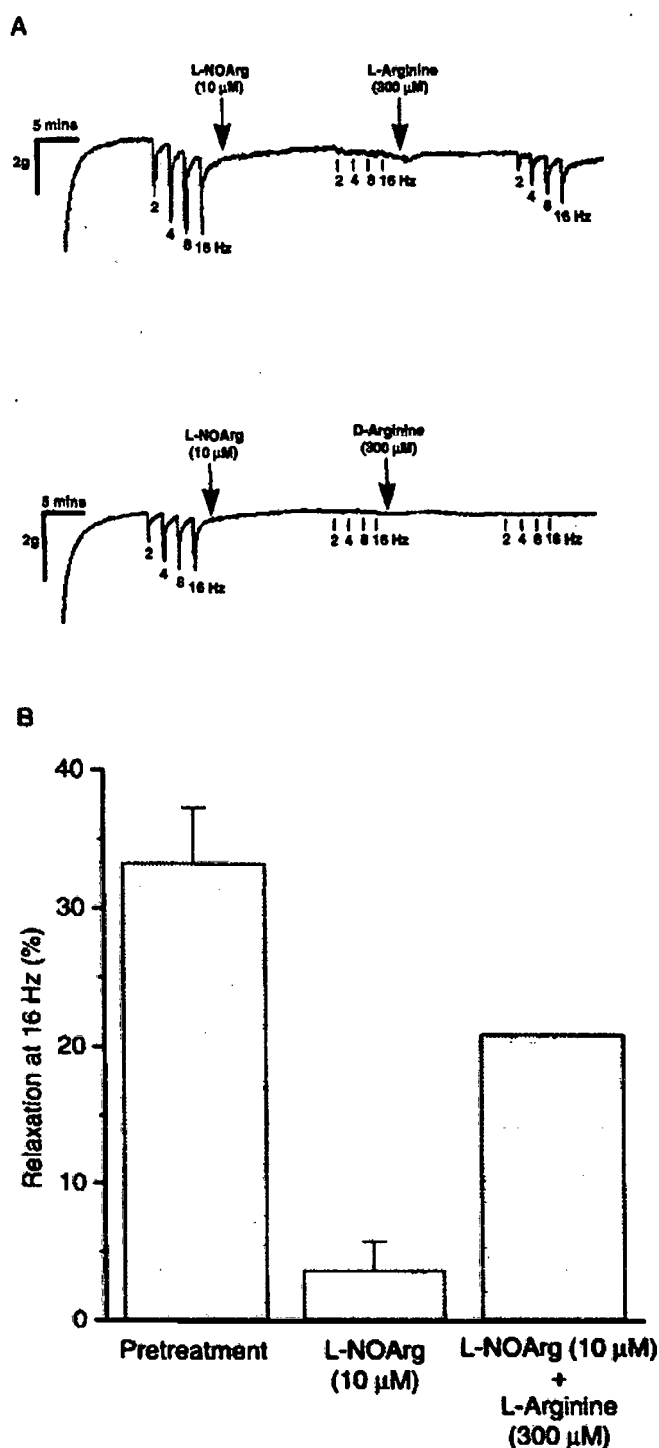


FIG. 2. Effects of L-NOArg, an inhibitor of NO-synthase, on relaxation of HCC tissue induced by EFS. HCC tissue strips were precontracted with phenylephrine (10 μM). Relaxation responses to EFS were determined at frequencies of 2, 4, 8 and 16 Hz under control conditions, after treatment with L-NOArg (10 μM), and then after further addition of L-arginine (300 μM) or D-arginine (300 μM). A, typical chart tracings showing inhibition of EFS-induced relaxation by L-NOArg and partial reversal by L-arginine, but not D-arginine. B, histogram showing inhibitory effect of L-NOArg on EFS-induced relaxation response at 16 Hz and partial reversal of inhibition by L-arginine. Data are shown as mean percent relaxation of the phenylephrine-induced tension, $\pm$ SEM ($n = 3$ tissue strips, $n = 2$ for L-arginine reversal).

cle, with a mean IC_{50} of 281 nM. Sildenafil inhibited PDE6 activity isolated from bovine retina with a mean IC_{50} of 33 nM, that is, 9-fold higher than that for inhibition of PDE5. In

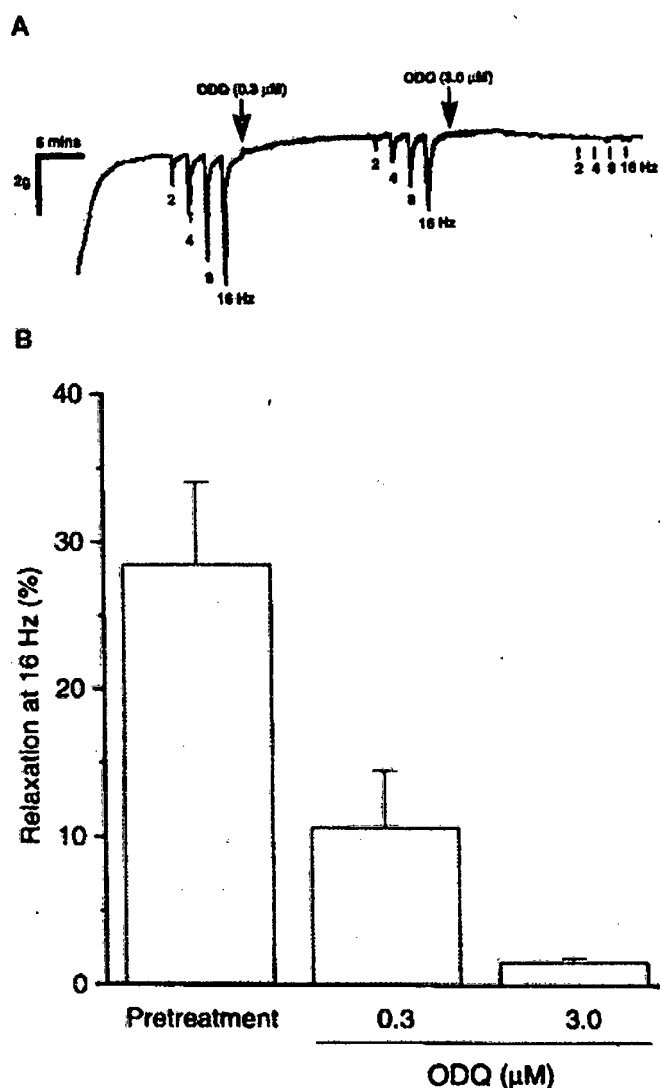


FIG. 3. Effects of ODQ, a selective inhibitor of soluble guanylate cyclase, on EFS-induced relaxation of HCC tissue. HCC tissue strips were precontracted with phenylephrine (10 μM) and relaxation responses to EFS were determined at frequencies of 2, 4, 8 and 16 Hz before and after treatment with ODQ (300 nM and 3 μM). Results shown are typical chart tracing and histogram of mean percent relaxation of phenylephrine-induced tension at 16 Hz, $\pm$ SEM ($n = 6$ tissue strips).

contrast, zaprinast was approximately twice as potent against PDE6 ($IC_{50} = 385$ nM) as against PDE5 (table 1).

Mode of inhibition of PDE5 by sildenafil. The rates of cGMP hydrolysis catalyzed by human platelet-derived PDE5 were determined across a range of concentrations of both cGMP and sildenafil to characterize the mode of inhibition of PDE5 by sildenafil. In the absence of sildenafil, the K_m for PDE5 was 1.6 ± 0.1 μM (mean $\pm$ SEM, $n = 7$ experiments). The extent of inhibition of PDE5 activity by sildenafil decreased with increasing cGMP substrate concentration. Lineweaver-Burk plots (fig. 8a) showed that sildenafil increased the apparent K_m for cGMP hydrolysis but had no effect on the apparent V_{max} , indicating a competitive mode of inhibition. The K_i for inhibition of platelet PDE5 by sildenafil was determined using Dixon analysis (fig. 8b), and a mean value $\pm$ SEM of 3.8 ± 0.2 nM was obtained ($n = 4$ experiments).

DISCUSSION

These in vitro studies have shown that sildenafil is a potent, competitive inhibitor of human PDE5. At sub-μM con-

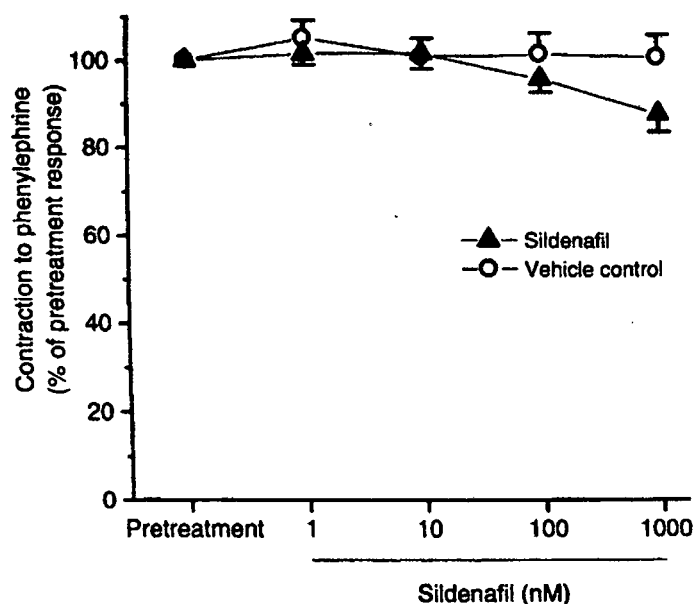


FIG. 4. Effect of sildenafil on magnitude of contractile response induced in HCC tissue strips by $10 \mu\text{M}$ phenylephrine. Contractile responses were normalized to pretreatment response, taken as 100%. Data points represent mean $\pm$ SEM for $n = 15$ tissue strips treated with sildenafil and $n = 9$ time-matched control strips from a total of 5 patients. Phenylephrine-induced tissue tension at pretreatment ranged from 2–7 gm.

centrations and in the absence of neurogenic stimulation, sildenafil had little or no relaxation effect on phenylephrine-contracted HCC tissue strips. However, sildenafil significantly enhanced the relaxation of isolated HCC tissues when neurogenic, NO-mediated relaxation was induced by EFS. In addition, sildenafil is a highly selective inhibitor of PDE5 relative to its activity against PDE1 to 4 and also shows selectivity (9-fold) over photoreceptor PDE6.

As a prelude to these studies, the system mediating EFS-driven relaxation of HCC tissue was characterized. Relaxation was completely blocked by tetrodotoxin, indicating that electrical stimulation triggered an exclusively neurogenic response. Consistent with earlier reports,^{8,20,21} we found that the majority of EFS-induced relaxation could be blocked by the selective NO-synthase inhibitor L-NOArg. The specificity of this effect was confirmed by the partial reversal of L-NOArg inhibition by a 30-fold higher concentration of L-arginine, but absence of reversal with D-arginine.

In earlier studies,^{8,20} methylene blue was used as an inhibitor of soluble guanylate cyclase to characterize the role played by cGMP in neurogenic NO-mediated relaxation of corpus cavernosum tissue, with 60 to 70% inhibition reported. However, methylene blue is a weak inhibitor of soluble guanylate cyclase, generates superoxide anions, and has other actions, such as inhibition of NO-synthase.¹⁶ In the present study, the guanylate cyclase inhibitor, ODQ, which has an IC_{50} of 10 nM,¹⁶ caused a 63% inhibition of EFS-induced relaxation at 300 nM and 95% inhibition at 3 μM . In addition, 300 nM ODQ completely inhibited the relaxation in vitro of phenylephrine precontracted HCC tissue induced by a maximally effective concentration (100 μM) of the NO-donor, sodium nitroprusside (unpublished data). Taken together, these findings further support the proposal that neurogenic NO and NO-donor induced relaxation of HCC is mediated exclusively through activation of soluble guanylate cyclase.

At concentrations of 10 nM and above, sildenafil significantly enhanced the neurogenic NO-mediated relaxation of HCC strips induced by EFS. The magnitude of the relaxation was a concentration-dependent manner.

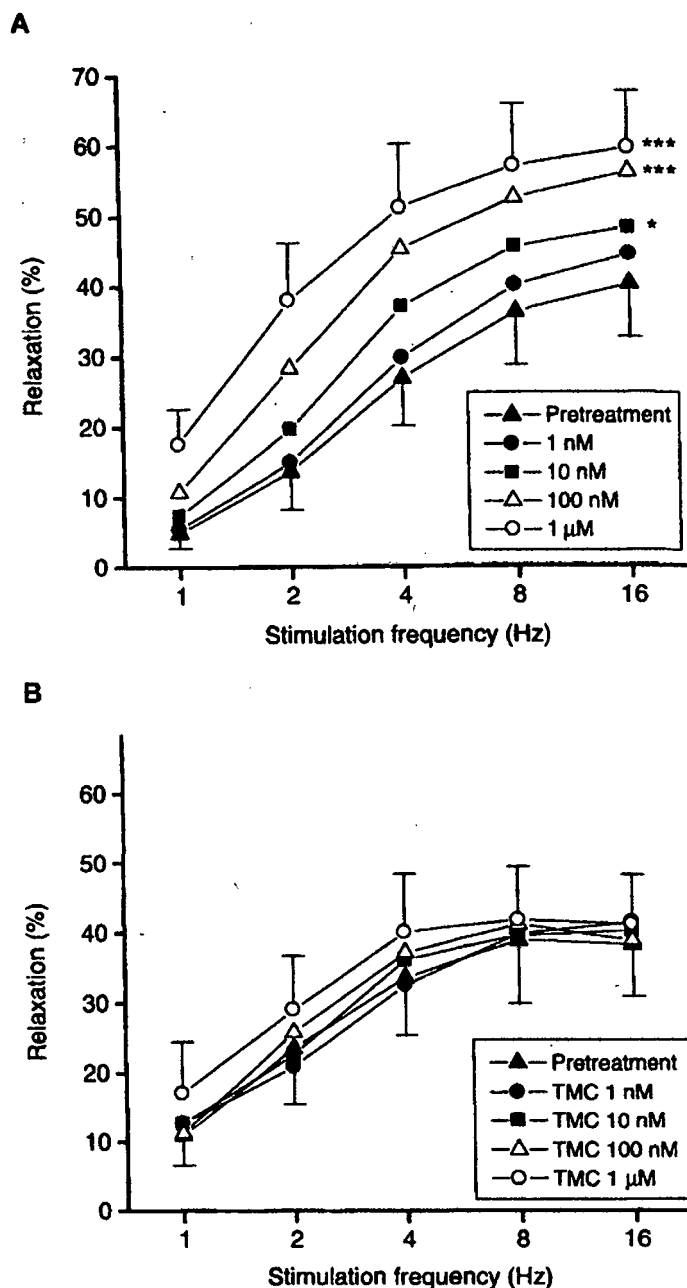


FIG. 5. Effect of sildenafil on EFS-induced relaxation of phenylephrine-precontracted HCC tissue strips. Tissues from 5 patients were incubated for 15 minutes with sildenafil (1 nM–1 μM) or vehicle (DMSO) and then precontracted with phenylephrine (10 μM) before EFS at frequencies 1–16 Hz. A, effects of sildenafil on tissue responses; B, responses for time-matched control tissues. Data points represent means of $n = 15$ tissue strips for sildenafil treatment and $n = 9$ for time matched controls. For the purpose of clarity, SEM values are shown only for pretreatment and 1 μM sildenafil treatments. Effects of sildenafil at 10 nM and above were significantly different from those of control groups as determined by covariance analysis: * $p < 0.05$; *** $p < 0.001$.

The effect on the magnitude of relaxation is qualitatively similar to that reported for zaprinast, another PDE5 inhibitor, at concentrations of 1 to 3 μM .^{7,8} However, sildenafil was effective at concentrations two orders of magnitude lower than zaprinast, consistent with its 240-fold higher potency against PDE5.

In addition to the findings with respect to the effect of sildenafil on the magnitude of response, this is the first study to demonstrate that an inhibitor of PDE5 can also prolong the relaxation response of corpus cavernosal tissue to nerve stimulation. It is postulated that sildenafil elicits this effect

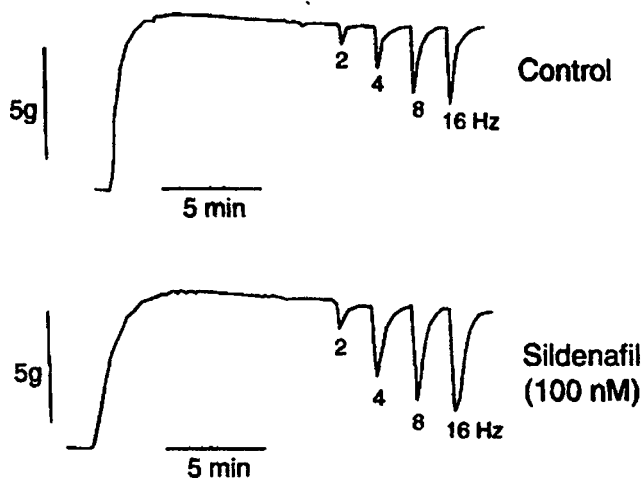


FIG. 6. Typical chart tracing showing the effects of sildenafil (100 nM) on magnitude and duration (peak width) of relaxation of phenylephrine precontracted HCC tissue strips induced by EFS for 10 seconds at frequencies of 1–16 Hz.

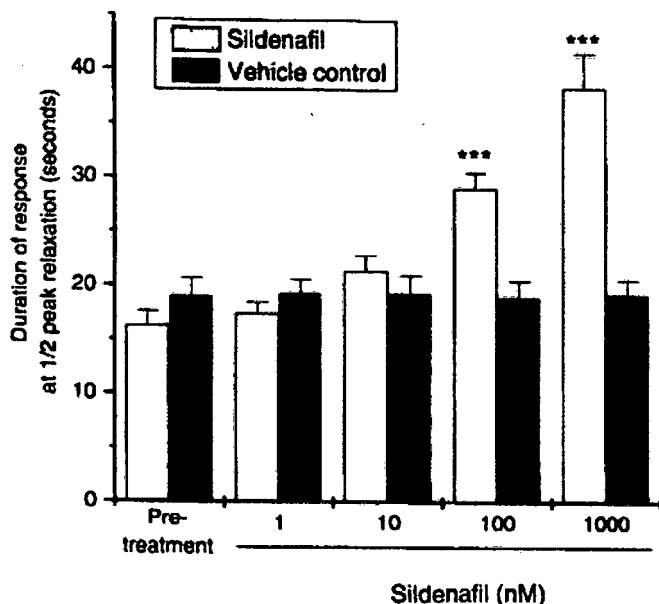


FIG. 7. Effects of sildenafil on duration of relaxation responses induced by EFS at 8 Hz using phenylephrine precontracted HCC tissue strips. Data points represent mean $\pm$ SEM for $n = 10$ tissues treated with sildenafil and $n = 7$ tissues tested as time-matched vehicle controls from a total of 3 patients. Significant differences from control, determined by unpaired Student's t test, are shown by *** $p < 0.001$.

as a consequence of not only enhancing the elevation of cGMP during nerve stimulation but also by delaying its decline to basal levels when nerve stimulation is halted. These functional results, taken together with earlier studies reporting high levels of PDE5 activity in HCC^{12,22} and elevation of cGMP levels by sildenafil in rabbit corpus cavernosum during stimulation with a NO-donor,¹³ support the conclusion that PDE5 is the primary regulator of cGMP levels in the corpus cavernosal smooth muscle. Interestingly, in the absence of neurogenic stimulation, sildenafil had little effect on the contractile response to the adrenergic agonist phenylephrine. Its effects were only apparent when NO-dependent pathways were stimulated. This result suggests that sildenafil will induce or enhance erections during sexual stimulation, but will not lead to erections in the absence of any sexual stimulus. This proposal is supported by reports that,

in patients with erectile dysfunction, sildenafil enhances penile rigidity during visual sexual stimulation.^{12,16} In this respect, sildenafil differs from vasoactive agents, such as papaverine and prostaglandin E₁, which are administered by intracavernosal injection as treatments for erectile dysfunction and lead to erections even in the absence of sexual stimulus.

The functional enhancement of HCC relaxation by sildenafil in vitro was achieved at concentrations in the same range as the maximum free plasma concentrations (C_{max}) of sildenafil observed in patients given erection-enhancing oral doses of sildenafil in the range 25 to 50 mg.^{12,16} (15 to 30 nM, derived from data in Boolell et al.¹² and based on 4% free fraction in plasma; unpublished data).

Experiments to evaluate the inhibitory potency of sildenafil against a range of PDE enzymes have shown that sildenafil is a potent inhibitor of PDE5 from human corpus cavernosum and human platelets with high selectivity for

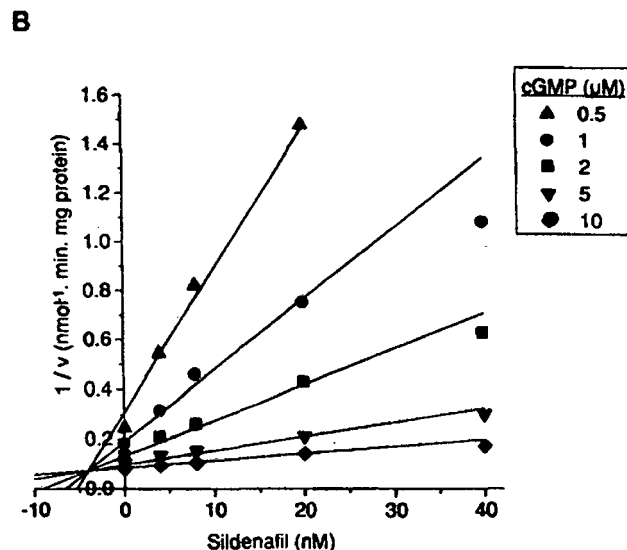
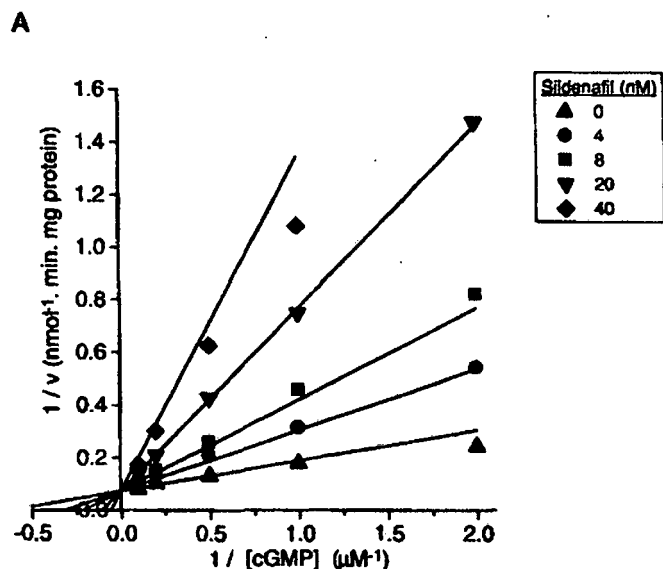


FIG. 8. Competitive inhibition of PDE5 from human platelets by sildenafil. Rates of cGMP hydrolysis catalyzed by PDE5 were determined using cGMP concentrations of 0.5–10 μ M and sildenafil concentrations of 4–40 nM. A, representative Lineweaver-Burk plot. B, data replotted according to procedure of Dixon ($1/v$ vs. $[I]$), with lines fitted according to competitive inhibition model. Each data point is the mean of three replicate assays and these results are typical of results obtained in four separate experiments.

TABLE 1. IC_{50} values for inhibition of human PDE isozymes 1-5 and bovine photoreceptor PDE6 by sildenafil and zaprinast

Compound	IC_{50} (nM)					
	PDE1	PDE2	PDE3	PDE4	PDE5	PDE6
Sildenafil	281 221-356 (n = 6)	>30,000 — (n = 4)	16,200 9500-27,800 (n = 4)	7680 5510-10,700 (n = 4)	3.5 2.5-4.8 (n = 15)	33 22-48 (n = 5)
Zaprinast	6650 6920-1445 (n = 3)	>100,000 — (n = 3)	>100,000 — (n = 4)	77,400 — (n = 2)	856 687-1065 (n = 8)	385 196-758 (n = 4)

n = number of experiments.

PDE 2, 3 and 5 were isolated from HCC, PDE1 from human cardiac ventricle and PDE4 from human skeletal muscle. IC_{50} values were determined using 0.5 μ M cGMP as substrate for PDE1, 2, 5 and 6, and 0.5 μ M cAMP as substrate for PDE 3 and 4. Data shown are geometric means with 95% confidence intervals.

PDE5 relative to PDE2 and PDE3, found in HCC, and also PDE1 and PDE4 (this study and ref. 12). The effects of sildenafil on photoreceptor PDE6 are reported here for the first time. Photoreceptor PDE6, which plays a key role in light-signal phototransduction, has similarity to PDE5 in terms of its specificity for cGMP as substrate, noncatalytic binding sites for cGMP, and sensitivity to inhibition by zaprinast.^{6,23} However, PDE6 isozymes have less than 60% amino acid sequence homology with PDE5 and can be distinguished from PDE5 biochemically on the basis of activation by trypsin and histone. PDE6 isozymes also have a significantly higher K_m for cGMP, on the order of 30 to 40 μ M.^{23,24} In this study, zaprinast, another cGMP PDE inhibitor, was approximately twice as potent against PDE6 as PDE5, consistent with an earlier report.²³ In marked contrast, sildenafil is almost an order of magnitude less potent against PDE6 than against PDE5. Consequently, at therapeutically relevant doses of sildenafil, any effects on visual function that might be a predicted consequence of PDE6 inhibition should be rare.

Human platelets are a readily available source of high levels of PDE5 enzyme¹⁷ and were used as the source of PDE5 for studying the inhibition kinetics of sildenafil. The platelet-derived enzyme preparation had a K_m for cGMP of 1.6 μ M, which is similar to values reported for PDE5 isolated from guinea pig lung (2.2 μ M)²⁵ and bovine lung (5.6 μ M).²⁶ Sildenafil was found to be a competitive inhibitor of PDE5 from human platelets with a K_i value, determined by Dixon analysis, of 3.8 nM. This indicates that sildenafil may bind at the catalytic site of PDE5 with high affinity, preventing access of the normal substrate (cGMP) and is in agreement with the proposal that the pyrazolo[4,3-d]pyrimidin-7-one nucleus of sildenafil mimics the guanosine base of cGMP.²⁷ The K_i value for PDE5 from platelets is similar to the IC_{50} of 3.5 nM obtained for inhibition of PDE5 from HCC, which was determined at a substrate concentration less than one third the K_m , where the IC_{50} for a competitive inhibitor will approximate to the K_i .²⁸

In summary, the results of the present study indicate that sildenafil is a potent, highly selective, competitive inhibitor of PDE5-catalyzed cGMP hydrolysis, and that it amplifies the neuronal NO/cGMP pathway involved in relaxation of HCC. Sildenafil, therefore, enhances the normal process leading to penile erection. The mechanism of action of sildenafil delineated in this study is consistent with the proven clinical efficacy of sildenafil in enhancing penile erections during sexual arousal in men with erectile dysfunction.^{12,15}

Acknowledgments. The authors thank Miss Samantha Allen for conducting the PDE5 enzyme kinetic studies.

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APPENDIX G-1

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Intracerebral haemorrhage associated with sildenafil citrate

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Sirs: Sildenafil is an orally active, potent and selective inhibitor of phosphodiesterase type 5 (PDE-5), an important regulator of cyclic guanosine monophosphate (cGMP) in the human corpus cavernosum which has recently been introduced for the treatment of erectile dysfunction. Sildenafil acts by increasing the concentration of cGMP in the corpus cavernosum smooth muscle cells leading to muscle relaxation, vasodilatation and penile erection [1]. Adverse effects include headache, visual and retinal disturbances, dizziness and a pupil-sparing third nerve palsy [2, 5, 7]. We report a patient who developed intracerebral haemorrhage (ICH) after sildenafil consumption.

A 67-year-old dentist was referred to our clinic in a confusional state together with speech, numeracy and memory disturbances. From the history it appeared that 5 days before admission, approximately 30 minutes after the ingestion of one tablet of sildenafil 25 mg, the patient complained of headache, confusion and nervousness without improvement in sexual function. One hour after the ingestion of the first tablet the patient took another 25 mg tablet, again without sexual intercourse. According to his wife, these symptoms increased together with language difficulty. The patient was

admitted to our department 5 days later. He had never used sildenafil before. The history revealed no arterial hypertension or migraine or haemostatic risk factors (e.g. use of anticoagulants or antiplatelet drugs, thrombolytic treatment), history of head trauma, hypercholesterolaemia, diabetes mellitus, pre-existing cardiovascular disease or cerebrovascular episodes such as stroke or transient ischaemic attacks. There was no family history of cerebral arteriovenous malformation, intracerebral aneurysms, or intracerebral haemorrhages. He had a 40-year history of tobacco abuse (approximately 15 cigarettes a day) and denied regular alcohol intake. He took no other medications.

On admission his blood pressure was 140/90 mmHg and pulse was 68/min. Neurological examination showed a right superior homonymous quadrantsopia and psychiatric examination a dysphoretic mood. Ophthalmoscopic examination was normal. Neuropsychological testing revealed a moderate impairment of compre-

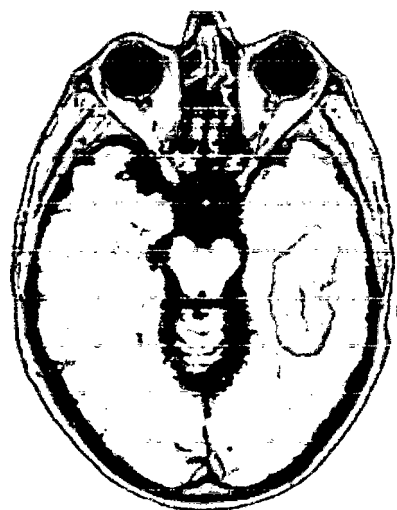


Fig. 1 Axial T1-weighted gadolinium-enhanced magnetic resonance imaging shows hyperintense signal lesion confined subcortically to the left temporal lobe

hension, naming, reading and writing with a relative sparing of repetition, acalculia, finger agnosia, colour anomia, and discrete involvement of episodic memory. Routine blood examination, platelet count and coagulation factors were normal, as well as electrocardiography, and colour-coded duplex sonography of extracranial vessels. Transcranial colour-coded duplex sonography revealed a sharply demarcated hyperchogenic area confined to the left temporal lobe. Two days after admission basal and gadolinium-enhanced T1-/T2-weighted cerebral magnetic resonance imaging revealed a large left temporal subcortical haemorrhage with moderate surrounding oedema (see Fig. 1). Although the chance of finding a clinically relevant vascular lesion in a patient 67 years old is very small, we would have liked to have performed cerebral angiography. However, the patient's wife, informed of the potential risk of cerebral angiography, refused her consent due to her husband's advanced age and the presence of a deep lobar ICH. The patient was treated with intravenous bolus of 1 g/kg mannitol, followed by 0.5 g/kg every 4 h for 7 days. He was discharged 5 days later with mild comprehension, reading, writing and episodic memory deficits, moderate acalculia, finger agnosia and colour anomia. The field defect was still present.

The close temporal relationship between sildenafil ingestion and onset of the neurological symptoms due to the ICH in a patient without a history of cerebrovascular accident or obvious risk factors for ICH suggest that sildenafil was causally related to the ICH. Smoking is currently not considered a primary risk factor for ICH [4, 6]. Since the symptoms started before any attempt at sexual intercourse, sexual exertion cannot be regarded

as the precipitating factor. Common adverse effects of sildenafil, such as flushing, headache and nasal congestion, indicate that vasodilatation is not confined to the corpus cavernosum [5]. On the other hand, the reported occurrence of acute myocardial infarction suggests that the drug may also act by redistributing the arterial blood flow, in turn reducing vessel perfusion [3]. The reported occurrence of headache, dizziness, visual disturbances, retinal dysfunction and a pupil-sparing third nerve palsy suggest that sildenafil also affects brain microvasculature regulation [2, 5, 7]. Recently, Ballard et al. [1] in an in vitro study have shown that sildenafil, in addition to a selective action on PDE-5, may also act on other two PDEs (i.e. PDE-1 and PDE-2) which are involved in the control of cerebral vasculature. In our case a particular susceptibility to the drug may have led to an abnormal, persistent vasodilatation of cerebral arteries and to an abnormal redistribution of arterial brain blood flow. Furthermore, our patient took a second 25 mg tablet within 1 h of ingestion of the first one, despite the manufacturer's advice suggesting

that the initial sildenafil dose in the elderly should be 25 mg. These factors may have increased the risk of a bleeding phenomenon in a subject with a senescent cerebral circulation. As cerebral angiography was not carried out in our patient, it remains unclear to what extent pre-existing cerebral microvascular disease contributed to the onset of ICH. However, although less accurate than cerebral angiography, brain magnetic resonance imaging and transcranial colour-coded duplex sonography did not show any cerebral malformations.

In conclusion, our case and the frequency of reported vascular adverse effects suggest that sildenafil should be used with caution in the elderly, especially when the minimum dose recommended by the manufacturer does not improve sexual function to first-time users. Longitudinal pharmacological studies in an elderly population are necessary to clarify this issue.

■ **Acknowledgements** R. M. was supported by a fellowship in Neuropsychology from Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST). This work was supported by MURST grants to R. C. The authors are grateful to Mrs. Gay Marks for help in the English revision of the manuscript.

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Coital Hemorrhage of an Arteriovenous Malformation after Premedication with Tadalafil (Cialis)

APPENDIX H-1

Thomas D.L. Steeves, MD,* Lyell K. Jones, MD,* Robert D. Ecker, MD,†
and Edward M. Manno, MD*

Phosphodiesterase type 5 (PDE 5) inhibitors are widely used in the treatment of erectile dysfunction. However, the results on the cerebral vasculature are unknown. Several cases of intraparenchymal hemorrhage in the setting of PDE 5 inhibitor use have been reported. The effect of these agents on the risk of arteriovenous malformation (AVM) hemorrhage is speculative. This report illustrates a possible association between tadalafil (Cialis, Lilly ICOS, Indianapolis, IN), a new long-acting PDE 5 inhibitor, and AVM hemorrhage during coitus. A 59-year-old male suffered a coital intraparenchymal hemorrhage after premedication with tadalafil. Angiography and magnetic resonance imaging demonstrated an underlying right temporoparietal AVM. The AVM was excised, and the patient made an uneventful recovery. AVMs are felt to be dynamic lesions that evolve in response to changes in blood flow. Repeated use of PDE 5 inhibitors could induce changes in an AVM that would make it more likely to hemorrhage, particularly in the setting of additional stress from coitus and elevated blood pressure. The potential for risk of devastating neurovascular complications related to PDE 5 inhibitors should be monitored. **Key Words:** Coital hemorrhage—arteriovenous malformation—tadalafil.

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More than 100 million men worldwide suffer from erectile dysfunction. In 1998, sildenafil citrate (Viagra), the first oral phosphodiesterase type 5 (PDE 5) inhibitor for the treatment of this condition, was approved. Since its introduction, sildenafil has been prescribed to more than 15 million men worldwide.¹ Its sales approach \$US 2 billion annually in a market whose value is expected to reach \$US 6 billion by the end of the decade.² In 2003, the FDA approved 2 new PDE 5 inhibitors: vardenafil (Levitra, Bayer, Pittsburg, PA), distinguished from sildenafil by greater biochemical potency, and tadalafil (Cialis, Lilly ICOS), which is unique for its prolonged half-life and extended window of efficacy.

PDE 5 is an isoenzyme of a family of cGMP hydrolyzing enzymes. It is located in vascular smooth muscle cells of the penile corpus cavernosum, as well as in various other human tissues, including the brain and cerebral arteries. In the corpus cavernosum, inhibitors of this enzyme permit cGMP to accumulate after its production in response to sexual arousal, which in turn relaxes the smooth muscle of the penile vasculature to allow vasodilatation and erection. The effect of these agents on the cerebral vasculature is unclear. Although PDE 5 inhibitors are not known to confer an increased risk of central nervous system hemorrhage, several cases of intraparenchymal hemorrhage associated with their use have been documented. Here we describe a case of coital hemorrhage of an arteriovenous malformation (AVM) after premedication with tadalafil.

Case Report

A 59-year-old right-handed man with a history of hypertension and erectile dysfunction presented to an outside emergency room after developing severe right-

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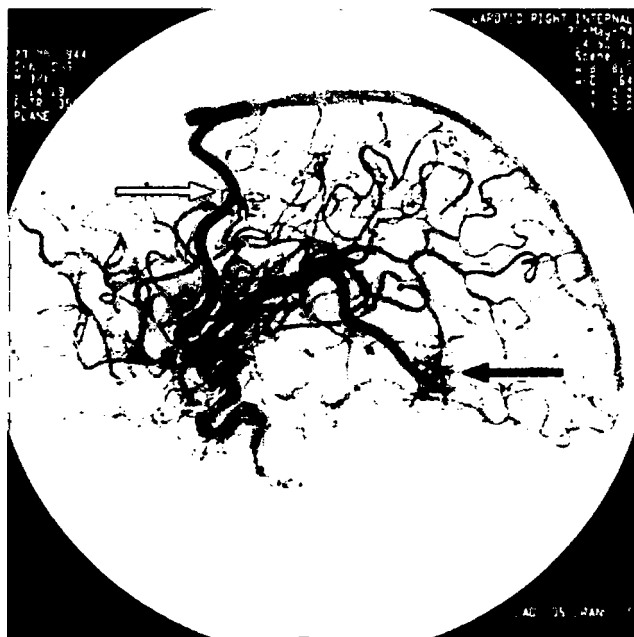


Figure 1. Appearance of AVM on angiogram. The right intracranial artery injection demonstrates a small AVM located in the superficial aspect of the posterior right temporal lobe (dark arrow) fed by a small branch of the angular artery. The arterial phase demonstrates a single superficial draining vein (white arrow) ascending laterally to empty into the superior sagittal sinus.

sided headache during intercourse. Two months before this incident, his primary care physician had prescribed tadalafil for erectile dysfunction, and the patient had used this medication several times with favorable results and no adverse effects. On this occasion he had taken 10 mg of tadalafil 2 hours before intercourse. He experienced no neurologic symptoms until intercourse, at which time he had an abrupt onset of a 9/10 right-sided posterior parietal headache. He discontinued his activity and took an aspirin as well as fexofenadine (Allegra, Aventis Pharmaceuticals, Bridgewater, NJ) for nasal congestion. He sought medical attention when his headache did not improve after approximately 1 hour.

On initial examination at his local hospital, the patient was found to be neurologically intact. However, a head computed tomography scan revealed an acute 3.5 cm × 4.5 cm × 6.5 cm bleed in the right temporoparietal area. The patient was transferred to the neurologic intensive care unit at our institution for further management. On arrival, his only neurologic deficits were a mild left pronator drift and an inconsistent visual field exam by confrontation that suggested a possible left homonymous hemianopsia.

Cerebral angiography (Fig 1) demonstrated a small AVM located in the superficial aspect of the posterior right temporal lobe fed by a branch of the angular artery. A single superficial draining vein ascended laterally to empty into the superior sagittal sinus. Magnetic resonance imaging (MRI) (Fig 2) showed a 4.2 cm × 4.8 cm ×

8.2 cm hyperacute intraparenchymal hemorrhage centered within the right temporal lobe and extending into the most anterior aspect of the right parietal lobe. Multiple enlarged vessels were seen in the sylvian fissure, as well as the previously noted superficial draining vein to the superior sagittal sinus. Formal visual field testing confirmed a complete left hemianopsia. The patient was taken to surgery, and the AVM was excised. He had an uneventful postoperative course and was discharged home with a resolving left-sided hemianopsia as his only remaining neurologic deficit.

Discussion

A number of adverse neurologic events are associated with sexual intercourse. Benign coital headache, vertebral and carotid artery dissection, and subarachnoid hemorrhage during coitus are all well known to neurosurgeons and neurologists. However, documentation of these events has been limited. Finelli³ reported a case of hemorrhage of a probable cavernous malformation during sexual intercourse in a hypertensive patient. More recently, several cases of intraparenchymal hemorrhage associated with sildenafil citrate, both with and without intercourse, have been described. Monastero et al⁴ reported a lobar hemorrhage associated with sildenafil but without intercourse. Buxton et al⁵ described a lobar hemorrhage after intercourse and premedication with sildenafil that ultimately resulted in the patient's death. Most recently, Marti and Masso⁶ described a midbrain hemorrhage occurring after premedication with sildenafil and intercourse, although the exact onset of symptoms in

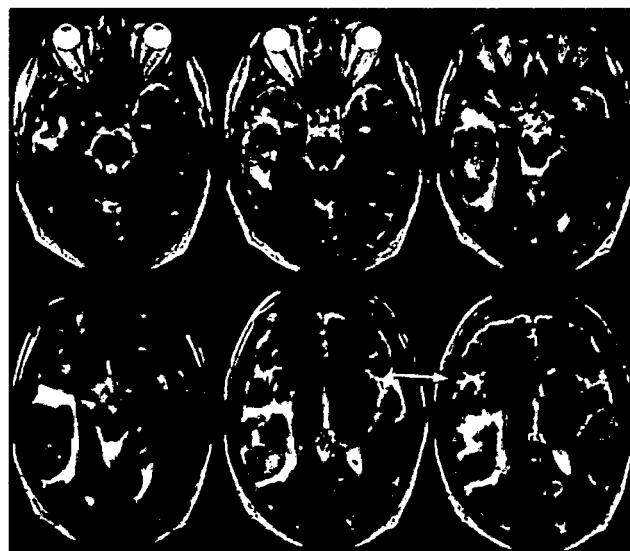


Figure 2. T2-weighted MRI demonstrating a large 4.2 cm × 4.8 cm × 8.2 cm hyperacute intraparenchymal hemorrhage centered within the right temporal lobe and extending into the most anterior aspect of the right parietal lobe. Multiple enlarged vessels are seen in the sylvian fissure as well as in the large superficial draining vein (white arrow) to the superior sagittal sinus.

relation to these events was not described. To our knowledge, no coital hemorrhage of an AVM in association with tadalafil, has yet been reported.

Our patient was a 59-year-old man with a history of moderate hypertension and an underlying AVM whose hemorrhage occurred during intercourse and after premedication with tadalafil. Given that the hemodynamic determinants of AVM hemorrhage have not been defined, to what extent these factors may have interacted to increase this patient's risk of hemorrhage is open to speculation.

Coitus is well known to have a marked effect on blood pressure in both normal and hypertensive subjects. Continuous intra-arterial blood pressure monitoring in ambulant hypertensive subjects has shown peaks values of up to 300/175 mmHg during intercourse, with a mean of 237/138 for men and 216/127 for women.⁷ In this context, it is possible that extreme hypertension alone triggered this man's hemorrhage, but the potential contribution of tadalafil to the presentation, whether directly or even indirectly by permitting him to engage in intercourse, also should be considered.

The adverse effect profile of all PDE 5 inhibitors is similar and includes headache, facial flushing, gastroesophageal reflux, nasal congestion, and visual disturbances. Tadalafil is also associated with myalgias and back pain, although the mechanism behind these symptoms is unclear. The effects of these agents on the intracranial vasculature are still being elucidated. Tadalafil has greater selectivity than sildenafil for PDE 5 compared with the other PDE isoenzymes.^{1-6,8} But Kruuse et al⁹ have shown that PDE 5 is present in the cerebral arteries of both rodents and humans, and that in vitro rodent cerebral arteries dilate in response to PDE inhibitors. However, in a more recent human study evaluating the effects of sildenafil on cerebral blood flow, Kruuse et al¹⁰ detected no changes in middle cerebral artery diameter as measured with Doppler ultrasound and no change in cerebral blood flow as measured with single-photon emission computed tomography.

The potential effects of the PDE inhibitors on AVM likewise have not been established; however, increased blood flow is known to produce progressive vessel changes in experimental models of AVMs. Tears in the internal elastic lamina of the afferent artery occur after 2-5 days of high flow, and further changes progress to involve all layers of the vessel to the point where it can no

longer be identified as an artery or a vein.¹¹ It remains possible that repeated use of PDEs, particularly those with prolonged half-lives such as tadalafil, could induce changes in an AVM that would make it more likely to hemorrhage when additional stresses from exertion and elevated blood pressure were placed on it. This is precisely the scenario that would be repeated time and again with the chronic use of tadalafil in sexual intercourse. Given the increasing popularity of these agents and the potential for their widespread use and abuse as performance enhancers even among relatively young individuals who do not suffer from erectile dysfunction, the risk of devastating neurovascular complication should be monitored.

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Sudden deafness from stroke

To the Editor: I was fascinated by the report by Leussink et al.¹ and how their patient, following a stroke, became suddenly and totally deaf, but had no realization that this was the case. This singular unconsciousness of a deficit is reminiscent of Anton syndrome, in which patients with cortical blindness may not only fail to realize that they are blind, but strenuously maintain that they can see perfectly. When, as inevitably happens, they blunder into objects, they immediately explain such accidents by confabulations ("the furniture has been moved," "the light is bad"). One is tempted to see Leussink and colleagues' case as an example of auditory Anton syndrome. It would be valuable to have more information about this patient. How, for example, did she explain her inability to understand people's speech? Did she confabulate reasons for this, like someone with Anton syndrome? And what, in retrospect, did she make of her strange week of cortical deafness after she had recovered her hearing?

Oliver W. Sacks, MD, *New York, NY*

Reply from the Authors: We feel honored and thank Dr. Sacks for his interest in our case¹ and his suggestion that our patient could have had Anton syndrome of the auditory system. With the publication space limitation, we could not mention all the details.

At first presentation, the prevailing impression that our patient gave was that of a perplexity and helplessness. She realized the effort that her family and medical staff made to communicate with her. In the first hours, she just seemed to realize that there was something wrong with her without being able to address the problem.

After some hours, noticing lip movements in these people, she would look at the person saying "I cannot hear you," but thereby

did not fully realize that this was part of the more general problem of not being able to hear at all.

While under investigation for auditory brainstem potentials, she would take off the headphones and look at them as if to say "What is this for?" or "What do you expect me to do with it?" She would then stand up from the examination chair and walk away. Concurrently, there was additional difficulty in communication, which we later formally established as a moderate fluent Wernicke type of aphasia. In this context, she would later repeat part of the sentences said to her (always with a question tone as if she was still uncertain of what she had grasped). On dictation, she much preferred to write down the end of sentences and missed the beginning as if the auditory system (or verbal understanding) needed to be slowly tuned up.

The condition substantially improved within 24 hours and subsequently continued to improve. After a few days she told people who set out to communicate with her that she could not hear well. Her premorbid below average level of intelligence probably did not permit her to carefully reflect and communicate the more complex nature of her initial problem. We have no recollection of her interpretation of the initial type of disturbance.

From all these features, we firmly believe that the patient at least initially had a cortical dysfunction that went beyond simple hearing loss. However, with aphasia interfering we are not certain that there was substantial anosognosia associated with it.

Markus Naumann, MD, *Augsburg, Germany*; Karlheinz Reiners, *Würzburg, Germany*

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Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra)

To the Editor: McGee et al.¹ report a case of intracerebral hemorrhage (ICH) with vardenafil in a 66-year-old Caucasian male with erectile dysfunction (ED) who had previously used sildenafil. This event has to be viewed within the context of the occurrence of ICH that has been reported with the other currently available phosphodiesterase-5 (PDE-5) inhibitors.

As a point of comparison, McGee et al. cited two reported cases of ICH associated with sildenafil, with a third case reported in 2004.² In contrast, there was one case of ICH with tadalafil, which was recently reported.³ These five reports cite cases of ICH associated with the use of PDE-5 inhibitors.

Worldwide utilization data for sildenafil and tadalafil and US data for vardenafil totals approximately 18.5 million men who have used a PDE-5 inhibitor for ED (according to information from the McGee article, a Medical News Today news brief dated June 3, 2004 available at www.medicalnewstoday.com/news-search.php?newsid=9046, and a press release dated February 26, 2004 available at www.gsk.com).

The worldwide incidence of ICH has been estimated to range from 10 to 20 cases per 100,000 population; in the US, the annual incidence of ICH (adjusted for age, sex, and race) is estimated at 15 cases per 100,000 population.^{4,5} Used as a point of reference, these numbers show that the risk of ICH among patients using the currently available PDE-5 inhibitors for ED is not considerably different from the general population.

The issue of causality and association of vardenafil with ICH may be difficult to ascertain in this patient in the McGee article because of the following confounders: although rare, ICH has been reported for all 3 PDE-5 inhibitors; the specific doses and duration of therapy with the previously used PDE-5 inhibitor (sildenafil) were not given; although no history of drug use was mentioned, a toxicology screen was not conducted; and a multiplicity of risk factors are involved in the etiology of ICH.⁶

Appropriate use of therapeutic agents includes a benefits-to-risk analysis by the clinician, with a clear and concise explanation given to the patient. The patient should also be informed that ED is often associated with endothelial dysfunction and may be a marker for cardiovascular disease.⁶

Wayne J.G. Hellstrom, MD, *New Orleans, LA*

Reply from the Authors: We appreciate Dr. Hellstrom's response to our article¹ and agree with all of his points. When assessing whether or not a side effect is related to a medication, timing of onset of symptoms in relation to ingestion of drug is important in addition to whether symptoms recur when the patient takes the drug again. Today, serious side effects of medications are difficult to prove since patients are reluctant to rechallenge themselves with a drug they believe was implicated in causing their symptoms. Therefore, we are left with the timing of onset of symptoms to ingestion.

Although we, the authors, are at a loss to hypothesize a mechanism of causation of ICH in our patient, our intention was to alert the medical community to this possible association through publication.

Robert A. Egan, MD, Hall T. McGee, MD, Wayne M. Clark, MD, *Portland, OR*

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APPENDIX 1-2

Reading impairment in the neuronal migration disorder of periventricular nodular heterotopia

To the Editor: We read with interest the report by Chang et al.¹ on the association of bilateral periventricular nodular heterotopia with seizures and impaired reading in people with normal intelligence.

We performed extensive neuropsychological testing on a 16-year-old boy with a left periventricular heterotopia and left temporal lobe dysplasia diagnosed by MRI and did not find any evidence of reading disability. Our patient came to evaluation because of academic difficulties. At the time of testing he had focal epilepsy which was well-controlled on lamotrigine. On the Wechsler Intelligence Scale for Children-III Edition, he had a Full Scale intelligence quotient (IQ) of 104, a Verbal IQ of 114, and a Performance IQ of 93. His Processing Speed Index was 64 (1%). On the Gray Oral Reading Test-4, his Reading Quotient was 103 (58% for age) with adequate reading rate, accuracy, frequency, and comprehension for age. On the Luria Nebraska Neuropsychologic Battery- Form 1, none of the 11 clinical scales or 5 ancillary scales were above the critical level of sixty-one. On the Wide Range Achievement Test-III, his reading standard score was 94 at the high school level (34%).

Our patient had normal reading ability. His slow processing speed contributed to his academic difficulty. This case supports the trend described by Chang et al. that patients with fewer

heterotopia show less cognitive impairment. We hypothesize that children with unilateral periventricular heterotopia may be less likely to develop reading impairment than children with bilateral heterotopia because there is less cortical involvement.

Deborah K. Sokol, Meredith R. Golomb, Karen S. Carvahlo, Mary Edwards-Brown, *Indianapolis, IN*

Reply from the Author: We appreciate the interest of Sokol et al. in our findings.¹ Their results support our demonstration of a relationship between the anatomical distribution of heterotopia and the cognitive consequences. Our study did not include any subjects with only a single heterotopic nodule or with other coexistent malformations, as in her case. We believe there are many potential mechanisms by which the presence of gray matter heterotopia could lead to a specific cognitive deficit, and further work is required to clarify them.

Bernard S. Chang, MD, *Boston, MA*

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Excess of serum copper not related to ceruloplasmin in Alzheimer disease

To the Editor: I read with interest the article by Squitti et al.¹ I am uncertain of the significance of the non-ceruloplasmin bound copper in the serum of Alzheimer patients. Is it simply a consequence of Alzheimer disease (AD) activity or is directly implicated in the disease process?

AD appears to have free copper unbound by ceruloplasmin in increased amounts. This may have clinical implications since treatment with clioquinol, a metal-protein-attenuating compound which inhibits zinc and copper ions from binding to Abeta and promotes Abeta dissolution, resulted in minimal deterioration of cognitive scores in treated patients compared to substantial deterioration in patients treated with placebo.²

Depleted copper levels have been noted to reduce APP production in animals and it is thought the APP regulation of production may represent a target for treatment of AD.³ The amyloidogenic pathway for Abeta peptides is initiated by BACE1. BACE1 interacts with the copper chaperone for superoxide dismutase-1 and reduces activity of superoxide dismutase through competition for available copper chaperone for superoxide dismutase.⁴

Intracellular copper homeostasis is very regulated, since free cuprous ions react with hydrogen peroxide to yield hydroxyl radical. Copper is imported by plasma membrane transport protein and rapidly binds to intracellular copper chaperone proteins. Amyloid precursor protein may be a copper chaperone protein⁵ and defective-free cuprous ions would be available to react with hydroxyl radical, a potent oxidative agent. Copper may interact with multiple mechanisms implicated in AD.

Steven R. Brenner, *St. Louis, MO*

Reply from the Authors: We thank Dr. Brenner for his letter and agree with all the issues raised. Cues to a direct implication of copper in the pathogenetic process leading to AD, rather than this metal being altered as a mere consequence of the disease process, have been given by a number of clinical trials conducted over the past 15 years.^{2,6,7}

These trials have provided encouraging results indicating that "metal-protein-attenuating-compounds" can indeed positively modify the natural history of AD. The chelating compound desfer-

rioxamine⁸ has demonstrated actual disease slowing effects, while a similar trend has also been shown with the use of clioquinol.² However, treatment duration appears to be a fundamental factor, as can it be expected with disease modifying compounds rather than symptomatic approaches.

The administration of clioquinol to AD patients for 36 weeks has provided encouraging results, yet these have been far less important than those obtained by the use of desferrioxamine for 24 months. In addition, a 24-week trial with D-penicillamine⁷ showed positive effects in reducing, during the administration phase, the oxidative stress that was present at baseline in AD patients. However, a significant cognitive effect could not be demonstrated in this short observation period due mostly to lack of measurable cognitive deterioration in the placebo group.

We agree with Dr. Brenner that copper is metabolically very finely regulated by the organism and that is precisely why we believe that even a small increase of the serum low molecular weight component can be of a great significance, particularly over a long period of time. When copper is bound to low molecular weight copper compounds, it can be easily exchanged among albumin and small transporter molecules such as peptides or aminoacids.⁹ This lability can potentially render copper more toxic and promote oxidative stress, which is significant because these low molecular weight components can easily cross the blood brain barrier.

The putative chaperone role of the Amyloid Precursor Protein (APP) has been shown and may be confirmed by our recent observations (manuscript in preparation) demonstrating a relationship between serum levels of copper unbound to ceruloplasmin and beta amyloid in the cerebrospinal fluid in AD patients.

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APPENDIX I-3

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Intracerebral hemorrhage associated with sildenafil use: a case report

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Sirs: Intracerebral hemorrhage (ICH) accounts for approximately 10% of all strokes and carries high morbidity and mortality. Causes of nonhypertensive intracerebral hemorrhage are arteriovenous malformations, aneurysms, amyloid angiopathy, coagulopathies and drugs. Drug-induced ICH occurs mostly due to anticoagulants, thrombolytics, sympathomimetics, metamphetamine and cocaine. To our knowledge, there are two previous reported cases about the relationship between sildenafil use and ICH [1, 2]. Here we report a case of ICH after a single dose of sildenafil use.

A 62-year-old, right-handed male was admitted with left-sided weakness and numbness. He reported that he had taken 50 mg of sildenafil two hours previously and had noticed numbness and weakness in his left arm and leg an hour after taking the drug. This was the first time he used the drug which was prescribed by a urologist. He indicated that the symptoms devel-

oped before any attempt for sexual intercourse which rules out the possibility of sexual exertion being the precipitating factor. On admission, his blood pressure was 150/90 mmHg and on neurological examination left hemiparesis, hemihypoesthesia, and hemihypoalgesia were evident. Cranial CT and MRI showed hemorrhage in the right thalamus, and the posterior limb of the internal capsule (Fig. 1). Intracranial and extracranial MRA were normal. He had a history of mild hypertension but he was not on any antihypertensive treatment. The patient was admitted to the stroke unit and antihypertensive treatment was initiated. Systolic blood pressure was between 120–150 mmHg and diastolic between 80–90 mmHg during his stay. Neurological status improved in one week and at discharge, he only had mild clumsiness of the left hand.

Sildenafil is a selective phosphodiesterase-5 (PDE-5) inhibitor. As a result of PDE-5 inhibition, cyclic

guanosine monophosphate (cGMP) increases in the vascular smooth muscle of corpus cavernosum, leading to muscle relaxation and vasodilation. Several studies have shown that NO-cGMP pathway may be responsible for cerebral vasodilation by similar mechanisms [3]. Recently, Ballard et al. have suggested that sildenafil acts on PDE-1 and PDE-2 which are involved in the control of cerebral vasculature [4]. The increase in the blood flow may have raised the risk of ICH.

Furthermore, it is advised that the initial sildenafil dose in the elderly should be 25 mg. Our patient had taken 50 mg of the drug as the initial dose which might have been another factor increasing the risk of ICH. Sildenafil may be the cause of the intracranial bleeding in our patient although a chance association cannot be ruled out.

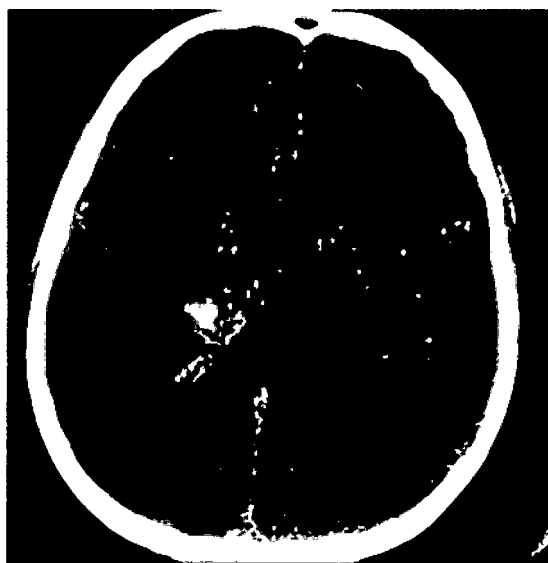


Fig. 1 Hematoma in the right thalamus and the posterior limb of internal capsule

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INTRACEREBRAL HEMORRHAGE ASSOCIATED WITH USE OF TADALAFIL (CIALIS)

Tadalafil (Cialis; Eli Lilly, Indianapolis, IN), a phosphodiesterase type 5 (PDE5) inhibitor, is used to treat erectile dysfunction in men. The most common adverse effects reported include headache, dizziness, minor visual changes, and ischemic optic neuropathy.¹ We describe a patient who developed intracerebral hemorrhage after taking two tablets of tadalafil 20 mg.

Case report. A 70-year-old man presented to our emergency department with headache, nausea, and vomiting lasting for 4 days. He was anxious and confused, with memory disturbances, but neurologic examination was otherwise normal. His medical history included prostate cancer, erectile dysfunction, and depression. There was no history of hypertension, head trauma, or prior cerebrovascular disease (stroke/TIA), and no underlying vascular or hemostatic risk factors. Blood pressure and pulse measured were 132/65 mm Hg and 78 bpm. A head CT scan without contrast showed an intracerebral hemorrhage (2 × 4 cm in diameter) in the right temporal lobe (figure, A). During admission the patient volunteered that he had taken two tablets of tadalafil 20 mg (total 40

mg) to enhance his sexual performance 1 hour before onset of his acute headache and that his symptoms worsened moderately during his sexual intercourse. A head CT angiography showed no vascular anomalies or malformations. The patient was discharged after 7 days with no further headache and improvement of his neurologic symptoms. A brain MRI/angiography performed 1 month after admission revealed the hypointense lesion with a surrounding rim of hyperintensity on T1-weighted images, with no contrast enhancement and no evidence of underlying vascular malformation (figure, B).

Discussion. Tadalafil (Cialis), sildenafil (Viagra, Pfizer Ltd.), and vardenafil hydrochloride (Levitra, Bayer Pharmaceutical Corp.) are phosphodiesterase type 5 (PDE5) inhibitors approved for the treatment of erectile dysfunction: they enhance penile erection by relaxing smooth muscles and increasing blood flow in the corpus cavernosum. Various side effects associated with the use of these medications have been reported: headache, facial flushing, hypotension, and dizziness. Minor visual changes and ischemic optic neuropathy with subsequent loss of vision are also described as side effects of these drugs.¹ Rare hemorrhagic adverse

Figure Axial head CT scan and brain axial magnetic resonance T1-weighted image



(A) Axial head CT scan image shows an intracerebral hemorrhage in the right temporal lobe (2 × 4 cm in diameter). (B) Brain axial magnetic resonance T1-weighted image performed 1 month after admission shows a hypointense lesion with a surrounding rim of hyperintensity.

APPENDIX

K-2

events include epistaxis and bleeding from esophageal varices and from hemorrhoids.² Cerebrovascular hemorrhage is extremely rare, but has been described after ingestion of sildenafil and vardenafil.^{3,4} Although cerebral amyloid angiopathy is a potential cause of intracerebral hemorrhage in the elderly, in our patient's history there was no genetic risk factor and no evidence of old petechial bleeds on MRI; the onset of neurologic symptoms within a narrow time window after taking tadalafil suggests the hypothesis of a strict correlation between hemorrhage and drug abuse. In our case, we hypothesize that the abuse of this drug may have altered cerebral autoregulation with resultant abnormal cerebral arterial vasodilation followed by regional cerebral ischemia, infarction, and subsequent hemorrhage. Only three case reports of intracerebral hemorrhage after PDE5 inhibitor medications have been described; our case suggests that tadalafil should be used at the dose recommended by the manufacturer. In our case, the trigger for intracerebral hemorrhage appears to have been the ingestion of two tablets of tadalafil 20 mg, despite the manufacturer's advice (recommended

starting dose 10 mg). This potential adverse effect should be considered by physicians involved in the treatment of patients with erectile dysfunction.

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GASTROINTESTINAL TRACT INVOLVEMENT ASSOCIATED WITH THE 3243A>G MITOCHONDRIAL DNA MUTATION

Defects of the mitochondrial genome (mtDNA) are increasingly recognized as common causes of neurologic syndromes.¹ One of the most common pathogenic mtDNA mutations is the m.3243A>G in the *MTTL1* gene. In addition to numerous neurologic features this mutation can also give rise to gastrointestinal symptoms including bloating, dysphagia, recurrent vomiting and anorexia, chronic diarrhea, and gastrointestinal pseudo-obstruction.^{2,4} To gain insight into the pathophysiology of gastrointestinal symptoms associated with the m.3243A>G mtDNA mutation, we investigated the degree of respiratory chain deficiency and the level of m.3243A>G mutation in individual areas from the gastrointestinal tract of two patients in whom gastrointestinal symptoms were both prominent and difficult to manage.

Case report. Patient 1 developed many features of the mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome including strokelike episodes, encephalopathy, myopathy, and lactic acidosis. In addition, she had a long history of digestive problems

dating back to childhood. She had a small appetite even as a child and felt full even with small portions. During her teenage years constipation became more marked, as well as a feeling of bloating after even a small meal. In later life she developed severe constipation requiring regular enemas and laxatives. She died at age 32 years.

Patient 2, who died at age 59 years, was the maternal aunt of Patient 1. She had a relatively late onset of symptoms, first presenting at the age of 43 years with migraine. She subsequently developed marked cognitive decline, cardiac failure, and deafness, but no strokelike episodes or seizures. She had few gastrointestinal problems in the early years of her disease course but constipation became progressively more severe over the last 5 years of life. She was given an altered diet, regular laxatives, and enemas, but even with these measures she became grossly distended with massive fecal loading.

At autopsy, the entire gastrointestinal tract from both patients was carefully examined and sampled. On gross examination, marked intestinal dilation was observed in Patient 2, accompanied by thinning of the bowel wall. In both patients, light microscopic examination revealed

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INTRACEREBRAL HEMORRHAGE ASSOCIATED WITH USE OF TADALAFIL (CIALIS)

Roberto Gazzeri, Massimiliano Neroni, Marcelo Galarza, et al.

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Case Report

Subarachnoid Hemorrhage and Intracerebral Hematoma due to Sildenafil Ingestion in a Young Adult

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Sildenafil citrate (Viagra®; Pfizer US Pharmaceutical Group, New York, NY, USA) is a potent vasodilating agent to treat male erectile dysfunction. Among its adverse effects, hemorrhagic stroke has not been widely reported yet. We present a case of a 33-year-old healthy man who ingested 50 mg sildenafil a half hour before onset of headache, nervousness and speech disturbance. Head computed tomogram of this stuporous man showed huge intracerebral hemorrhage and thick subarachnoid hemorrhage, but angiography failed to disclose any vascular anomalies. Subsequent surgical procedure was followed, and rehabilitation was provided thereafter. Sildenafil seems to act by redistributing arterial blood flow, and concurrent sympathetic hyperactivity, which lead to such hemorrhagic presentation. Extreme caution should be paid on even in a young adult male patient even without known risk factors.

KEY WORDS : Intracerebral hemorrhage · Risk factors · Sildenafil · Subarachnoid hemorrhage.

INTRODUCTION

For a decade, sildenafil citrate (Viagra®; Pfizer US Pharmaceutical Group, New York, NY, USA) has become one of the top-selling product in the world-wide market for male impotence treatment. Since its first introduction however, numerous adverse effects have been reported, and particular attention should be paid upon when prescription is considered. With regard to intracerebral hemorrhage (ICH), there are only four English written literatures^{1,4,9,10}. All of these cases showed minimal-to-moderate degree hemorrhage with unremarkable recovery.

We experienced a case of massive ICH associated with subarachnoid hemorrhage (SAH) requiring surgical removal. This young male patient did not have any risk factors for hemorrhage. A detailed case report and possible pathophysiologic explanations are presented.

CASE REPORT

A 33-year-old man was brought in to the Emergency Room for sudden unconsciousness following paroxysmal headache, nervousness and speech disturbance of two-hour duration. Approximately a half hour prior to symptom onset, he ingested one tablet of 50 mg sildenafil citrate to attempt sexual intercourse, but he could not.

Although he was slightly overweight (178 cm, 88 kg), he had been healthy and free of any significant medical history, including arterial hypertension, diabetes, hyperlipidemia, migraine, pre-existing cardiovascular or cerebrovascular diseases. He took no other medications, except episodic common-cold remedies. He had a 15-year history of tobacco smoking (approximately 1 pack per day), and ingested irregular alcohol about two times per week, presumably more than social drinking. He had been married 35 days before this event, and had taken sildenafil citrate 25 mg for two times during recent 2 weeks that were prescribed by a urologist. His wife denied any similar symptoms when used previously.

On admission, he was profoundly stuporous, densely quaternary (Grade 3/Grade 1), and had fully dilated pupils. Vital signs showed high blood pressure of 160/95 mmHg,

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APPENDIX L-2

Massive ICH due to Sildenafil | HS Byoun, et al.

rapid pulse rate (108/min) and respiration (24/min), and fever up to 38.5°C, respectively. Brain computed tomography (CT) showed a huge ICH on the right basal ganglia, intraventricular clots and thick SAH (Fig. 1). A CT angiography and transfemoral catheter angiography (TFCA) failed to disclose any vascular lesion on the corresponding hemisphere (Fig. 2).

Because of impending herniation, we hurried him into the operating room for decompression. Following dural reflection, swollen brain was encountered, and prompt temporal corticectomy was conducted to find organizing hematoma. After gentle suction and irrigation of hematoma, the sylvian fissure was widely split to show most course of the right middle cerebral artery (MCA). From distal portion, the MCA was thoroughly inspected up to the proximal MCA, but we could not find any aneurysmal dilatation or other angiomatous lesions. Meticulous hemostasis and expansive duroplasty was done. Skull flap was not covered to control raised intracranial pressure.

Postoperatively, he remained stuporous, but motor function was slightly improved (Grade 5/Grade 1). While in the intensive care unit stay, blood laboratory tests and serologic tests were undertaken, but there were no proven clues for the intracranial bleeding. Afterwards, robust rehabilitation was followed, and cerebrospinal fluid diversion and cranioplasty was performed for delayed hydrocephalus and skull defect, at postoperative 40 days (Fig. 3). At the last follow-up visit, 18 months postoperatively, he regained consciousness, was able to communicate with care givers in restricted extent, but was still hemiparetic (Grade 5/Grade 3) on wheel-chair and dependent for commanding major activities of daily living.

DISCUSSION

Causes of ICH in a non-hypertensive subject are largely divided into structural vascular anomalies (arteriovenous malformation, aneurysm, moyamoya disease, amyloid angiopathy), and dysfunctional coagulation (coagulopathy, drugs). Drug-induced ICH is mostly attributed to anticoagulants, thrombolytics, sympathomimetics, amphetamine, or cocaine¹¹. Although there are four previous reports about ICH after sildenafil use, all of these were manifested as minimal volume hemorrhage in elderly with risk factors and thus, surgical evacuation was not required^{1,4,9,10}. The present case mimics either diffuse, thick SAH from rupture of the proximal MCA aneurysm, or massive ICH leaking into the ventricles and subarachnoid space. With the aid of angiography, possibility of vascular anomaly was discarded. The cause and effect relationship of sildenafil and ICH herein,

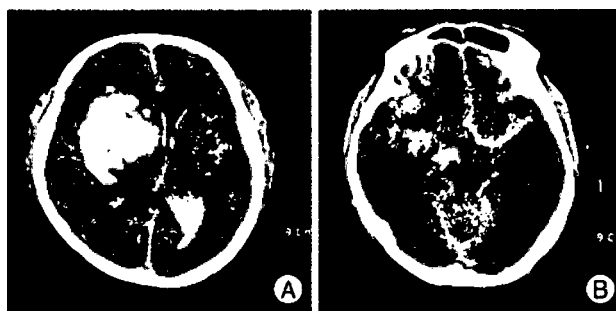


Fig. 1. Admission head computed tomograms show huge hemorrhage on the right basal ganglia and ventricles (A), in addition to diffuse subarachnoid hemorrhage (B).



Fig. 2. Right carotid angiograms only show displacement of the anterior and middle cerebral arteries without any anomalous cerebral vasculatures.

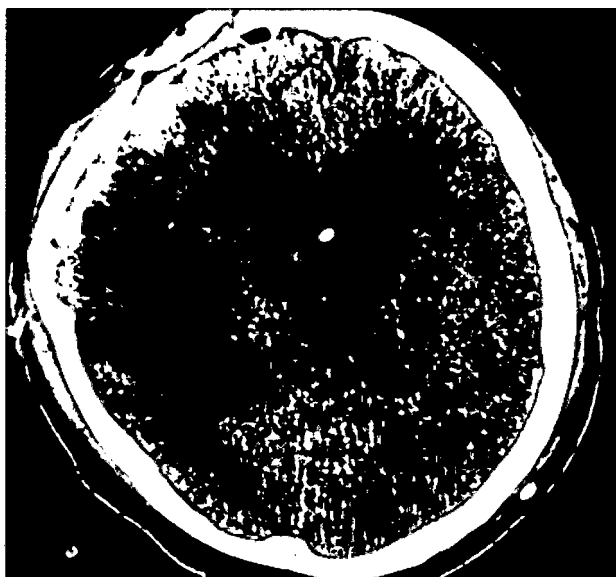


Fig. 3. A computed tomograms scan following cranioplasty and ventriculoperitoneal shunting obtained on postoperative 3rd day.

can be established when considering close temporal relationship between sildenafil ingestion and onset of neurological symptoms, within 2 to 4 hours of presumed peak level in blood, due to ICH in a patient without risk factors and non-specific blood laboratory results^{6,14}.

Sildenafil (UK-92,480), an orally active, selective inhibitor of phosphodiesterase type 5 (PDE-5), is a crucial regulator of cyclic guanosine monophosphate (cGMP) and at first

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intention, it is manufactured aiming at the corpus cavernosum of the human male. It plays a role in causing muscle relaxation, vasodilatation and penile erection by increasing concentration of cGMP and nitrous oxide (NO) in the smooth muscle of the corpus cavernosum³⁾. Side effects of sildenafil, including flushing, headache, nasal congestion, and changes in pulmonary blood flow can tell us that such vasodilatory effect is not confined to the corpus cavernosum^{11,12)}. This drug also redistributes the arterial flow, and decreases perfusion, consequently may lead to acute myocardial infarction. For the above reasons, it lowers systolic blood pressure by 8 to 10 mmHg in clinical trials¹⁴⁾.

Several ischemic manifestations, such as transient ischemic attack, ischemic stroke, cerebral infarction, or ischemic optic neuropathy can be explained by the above mechanisms⁶⁾. Vasodilatory effect of sildenafil may also cause atrial fibrillation, provoke atrial thrombi and cardioembolism in a pre-existing cardiomyopathic patient by increasing pressure gradient over the left ventricular outflow tract²⁾. On the other hand, hypotension could lead to secondary sympathetic hyperactivity^{8,12)}. Hypotension, cardiac arrhythmia, and rebound sympathetic hyperactivity seems to play concerted roles in producing stroke, especially in ischemic stroke. In previous literatures, we could not find any linear relationship between drug dosage (25 mg, 50 mg, 100 mg) and occurrence of stroke^{1,4,5,7-10)}. But, all cases were associated with utilizing more than 50 mg once or twice in a short period. An unknown process of sensitization may be involved however, the mode of drug action in large part, may be not cumulative but idiosyncratic.

The reported occurrence of headache, dizziness, visual disturbances, retinal dysfunction, and a pupil-sparing oculomotor palsy suggest that sildenafil affects regulation of the cerebral microvasculature. In addition to a selective action on PDE-5, sildenafil may act on other two types of PDE (PDE-1 and PDE-2), which are involved in control of cerebral vasculature^{6,13)}. To date, there has been no clear evidence to explain pertinent mechanisms of ICH associated with sildenafil.

In summary, sildenafil may act by redistributing arterial blood flow, hence rendering brain tissue more inappropriate perfusion, presenting as prodromes of headache, nervousness and speech disturbance as shown in the current case. Ensuing sympathetic hyperactivity through PDE-1 and PDE-2 might lead to rupture of vessels. Although it is contrary to common belief, we suggest that these inciting and propagating factors for ICH even in a young adult

male patient without known risk factors should be warned before prescribing sildenafil.

CONCLUSION

Sildenafil is a potentially dangerous drug, which can provoke life-threatening ICH and SAH in a young adult male. When considering usage, careful discussion and pre-medication work-up with urologist is mandatory. Adverse effect, such as headache, nervousness, dizziness or speech disturbance should be promptly diagnosed to minimize sequelae.

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Subarachnoid hemorrhage associated with tadalafil

Tadalafil is a phosphodiesterase type-5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction. Inhibition of the PDE5 isoenzyme, which is responsible for degradation of cyclic guanosine monophosphate in the corpus cavernosum, will ultimately enhance the effect of nitric oxide and, consequently, the relaxation of the vascular smooth muscle in the corpus cavernosum and penile erection after sexual stimulation. Tadalafil is the longest-acting PDE5 inhibitor, with an elimination half-life of 17.5 hours and up to 36 hours' duration of effect. The drug has been associated with headache, flushing, dizziness, visual disturbances, and hypotension.¹

A 45-year-old previously healthy man arrived at the emergency department with a severe headache of five hours' duration associated with one episode of vomiting. There was no decrease in the level of consciousness, no focal neurologic deficit, and no convulsive activity. The patient was previously healthy, with no history of diabetes mellitus, hypertension, cerebrovascular disease, trauma, or bleeding disorders and denied taking any prescription medication, over-the-counter medicine, or herbal products. The patient's family and social histories were unremarkable. On examination, he was agitated and in severe discomfort due to the headache. He reported tak-

ing one 20-mg tablet of tadalafil a few hours before the onset of symptoms and stated that he had started taking tadalafil recently "as needed" without consulting a health care provider. A computed tomography (CT) scan of his head revealed a subarachnoid hemorrhage (SAH) (3 × 4 cm in diameter); CT angiography of the head showed no vascular abnormalities or aneurysmal malformations. An electrocardiogram and a chest radiograph were normal, and all laboratory test values and vital signs were within normal limits. The patient had an uneventful four-day stay in the intensive care unit; he received 60 mg of nimodipine orally every four hours and was discharged home.

This patient's adverse reaction can be attributed to tadalafil because of the temporal relationship between use of the drug and the SAH. The probable association of the event with tadalafil use is enhanced by the fact that the patient had no risk factors for developing an SAH, and no underlying etiology was evident. Use of the Naranjo et al.² adverse-reaction probability scale revealed a probable association between the SAH and tadalafil (score of 6). In addition, a PubMed search about this probable association revealed two cases of intracerebral hemorrhage (ICH) associated with the use of tadalafil. Steeves et al.³ reported a possible associa-

tion between tadalafil use and arteriovenous malformation (AVM) hemorrhage during coitus in a 59-year-old man. The AVM was excised, and the patient made an uneventful recovery. Gazzeri et al.⁴ described an ICH in a 70-year-old man without evidence of any vascular anomalies who took 40 mg of tadalafil to enhance his sexual performance one hour before the onset of symptoms. The patient was discharged from the hospital after seven days with improvement in neurologic symptoms. Six cases of SAH or ICH have been reported after the ingestion of sildenafil,⁵⁻¹⁰ and a single case of ICH was reported in a patient taking vardenafil.¹¹

Tadalafil can inhibit PDE5, which is found in platelets. This can lead to the inhibition of platelet activation and aggregation.¹² On the other hand, nitric oxide induces relaxation of vascular smooth muscles. Platelet inhibition combined with increased cerebral blood flow may be associated with an increased risk of SAH.⁹ Although tadalafil has not been shown to increase bleeding times in healthy patients, the manufacturer recommends that caution be exercised in patients with bleeding disorders or significant active peptic ulceration.¹

Given the potential risk of hemorrhagic stroke after the ingestion of tadalafil, clinicians should be cautious when prescribing this medication and should consider this agent as a potential cause of cerebral hemorrhage in patients with no other underlying etiology or risk factors.

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A Web-based experiential rotation platform

Today's college students may require different approaches to teaching and learning. The so-called "video-game generation" currently populating the majority of pharmacy schools is adept at using technology and seems to respond well to interactive teaching techniques.¹ Efforts to increase the use of technology to engage students in learning have been met with some success.²⁻⁴ To date, little has been reported outside the classroom setting regarding the use of technology to individualize a student's experience or the integration of technology into the clinical experiences of a pharmacy residency program.⁵

Currently, several colleges of pharmacy use Web platforms to serve as a hub for students and preceptors at rotation sites.⁶ Our institution effectively uses this type of system to distribute important announcements, view student and preceptor schedules, and complete evaluations. Recently, we began exploring the use of a Web-based platform (Microsoft SharePoint, Microsoft Corp., Redmond, WA) to organize and shepherd students through common advanced pharmacy practice experiences (APPEs) at our institution, as well as coordinate the rotation experiences of pharmacy residents. For preceptors, this technology affords numerous advantages, which are described below.

Microsoft SharePoint is an integrated server program within the Microsoft Office system.⁷ This platform enables preceptors to customize a website specific to their rotation. Students are provided with immediate and ongoing access to the overall rotation description, expectations, and assignments.

One of the benefits of using this type of technology for experiential education is its customizability. Preceptors are free to upload documents, design student-controlled pages (e.g., blogs), and develop calendars. Users are granted permission to view, modify, and control content by the preceptor. We have chosen an approach that will allow each rotation site to have a similar structure

while maintaining preceptors' autonomy regarding content. This should provide some familiarity for students who have several APPEs. In addition, a core group of preceptors can facilitate a site template and design for those preceptors less comfortable with the process. Residents also frequently engage in these rotation experiences and can have materials and resources specific to their level of expertise and rotation objectives layered into each rotation site.

At its most basic level, the rotation website can be used to house the basic information a student or resident may need for the rotation experience. Links to the current syllabus, contact information, and a rotation calendar are common components of our rotation websites. Learning modules can add another layer of content to the website. Another approach to developing content for these Web pages may be to have each student or resident create a concise summary on a topic. This succinct, one- or two-page primer on a specific topic could serve as the initial content for each module. In combination with a library of representative readings and online resources, each module page can be a complete mixed media resource that students and residents can access at any point during the rotation experience.

SharePoint also enables the construction of "wiki" and blog pages. This function would permit students to keep a journal of their experiences for the month (e.g., unique patient cases encountered, drug information pearls learned, key concepts or queries that required time and effort to research). In addition, because the entire website is searchable, each topic recorded on the journal page is then part of the content on the site and viewable from the primary content pages.

As with any new educational tool, the effectiveness of this Web-based module will need to be assessed. We believe that two global areas should be addressed in the assessment of this type of educa-

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Subarachnoid and Intracerebral Hemorrhage After Alcohol Ingestion and Illicit Use of Sildenafil

Reçetesiz Sildenafil ile Alkol Kullanımı Sonrası Gelişen Subaraknoid Kanama ve Intracerebral Hematom

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ABSTRACT

Sildenafil is a drug used in the treatment of male impotence. Few cases of spontaneous intracerebral hemorrhage following the use of sildenafil have been cited in the literature. A 42-year-old man was admitted to the emergency outpatient clinic of Istanbul Educational and Research Hospital after sudden loss of consciousness. He had ingested alcohol, taken 50mg sildenafil and had sexual intercourse. Non-contrast cranial tomography revealed an intracerebral hematoma with extension to the ventricles.

Sildenafil is a selective phosphodiesterase-5 enzyme inhibitor. With the inhibition of PDE-5, the amount of cyclic-guanosine monophosphate (c-GMP) in the smooth vascular muscle cells in the corpus cavernosum increases, leading to a relaxation of muscles and vasodilatation. Studies have shown that the NO-c-GMP pathway leads to cerebral vasodilatation with a similar mechanism. The literature has shown that the effect of PDE-1 and PDE-2 on cerebral bleeding control is affected by sildenafil. This increased blood flow increases the risk of intracranial haemorrhage.

Although data concerning the presentation of intracerebral hematoma in connection with the combined use of alcohol ingestion and use of sildenafil is inadequate, it can nevertheless be thought that the combined use increases the risk of spontaneous intracerebral hemorrhage and caution is in order concerning the matter.

KEYWORDS: Sildenafil, Intracerebral, Hemorrhage, Alcohol, Subarachnoid bleeding

ÖZ

Sildenafil erkek impotansinin tedavisinde kullanılan bir ilaçtır. Sayısı az olsa da literatürde sildenafil kullanımı sonrasında spontan intraserebral hemoraji olguları bildirilmiştir. Kırk iki yaşında bir erkek hasta ani bilinç kaybı sonrasında İstanbul Eğitim ve Araştırma Hastanesinin acil polikliniğine başvurdu. Alkol alıp, 50mg sildenafil kullanmış ve cinsel ilişkide bulunmuştu. Kontrastsız kraniyal tomografi ventriküllere uzanan bir intraserebral hematoma gösterdi.

Sildenafil selektif bir fosfodiesteraz-5 enzim inhibitörüdür. PDE-5 inhibisyonu ile korpus kavernosumdaki düz vasküler kas hücrelerinde siklik guanozin monofosfat (c-GMP) miktarı artıp kaslarda gevşeme ve vazodilatasyona yol açar. Çalışmalar NO-c-GMP yolunun benzer bir mekanizmayla serebral vazodilatasyona yol açtığını göstermiştir. Literatür, PDE-1 ve PDE-2'nin serebral kanama kontrolü üzerindeki etkisinin sildenafilden etkilendiğini göstermiştir. Bu artmış kan akışı, intrakraniyal kanama riskini artırır.

Kombine alkol alma ve sildenafil kullanmayla bağlantılı olarak intraserebral hematoma ortaya çıkmasıyla ilgili veriler yetersiz olsa da kombine kullanımın spontan intraserebral kanama riskini artırdığı ve bu konuda dikkatli olmak gerektiğini düşünülebilir.

ANAHTAR SÖZCÜKLER: Sildenafil, Intracerebral, Kanama, Alkol, Subaraknoid kanama

INTRODUCTION

Sildenafil is a drug used in the treatment of male impotence. It has a direct effect on the vessels of the corpus cavernosum. Sildenafil acts on the corpus cavernosum by way of a raised concentration of c-GMP and NO in the smooth muscle cells. The increased c-GMP concentration leads to vasodilatation and the erection of the penis (7). In addition to this vascular reaction, other well-known side effects are flushing, headache and dizziness due to dilatation of the cerebral veins (10). Among its adverse effects, hemorrhagic stroke has not been widely reported yet (7). Although few cases of spontaneous intracranial hemorrhage following the use of sildenafil have been reported in the literature. We report a case of fatal

subarachnoid and intracerebral haemorrhage as a result of ingestion of alcohol and non-prescription use of sildenafil.

CASE REPORT

A 42-year-old man was admitted to the emergency outpatient clinic of Istanbul Educational and Research Hospital after sudden loss of consciousness. He was said to have ingested alcohol, taken 50 mg sildenafil and had sexual intercourse. On admission, blood pressure was 210/130 mm Hg and pulse 88 per minute. The Glasgow Coma Scale score was 5 (no eye opening, no verbal response and flexion to pain). Non-contrast cranial tomography revealed an anterior interhemispheric bleeding with extension to all four ventricles (Figure1, 2). An

APPENDIX N-2

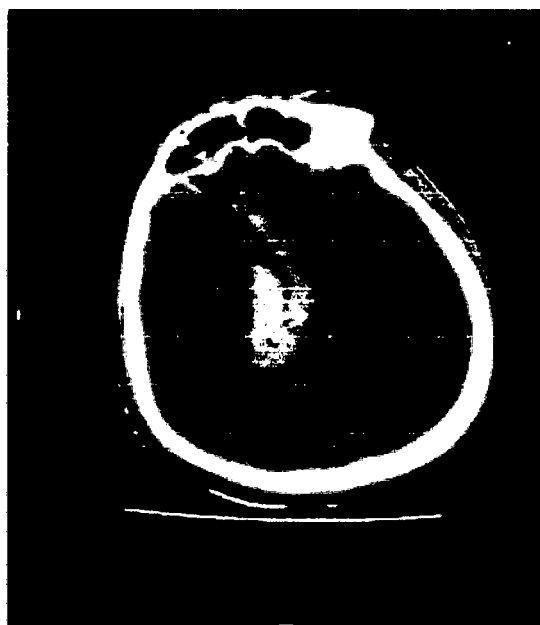


Figure 1: Non-contrast cranial tomography revealed an anterior interhemispheric bleeding with extension to all four ventricles (lateral ventricles).

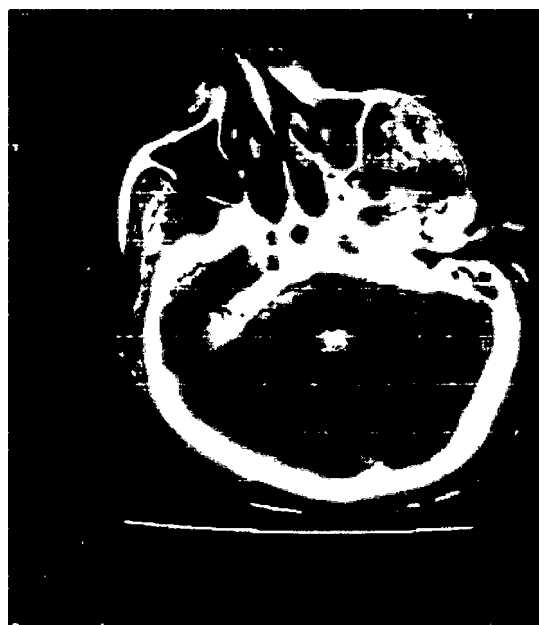


Figure 2: Non-contrast cranial tomography revealed an anterior interhemispheric bleeding with extension to all four ventricles (fourth ventricle).

angiography would have preferably been performed but the patient's condition did not allow this. No other tests related to an increased risk of stroke could be performed. An external ventricular drain was placed and the patient was taken to the intensive care unit but he failed to respond to maximal therapy and died.

DISCUSSION

The reasons of non-traumatic intracerebral hemorrhage can be categorised as hypertension, non-hypertensive gross structural vascular anomalies (AVM, aneurysm, MoyaMoya disease, amyloid angiopathy, etc.), intracranial neoplasms, cerebral venous thrombosis, infection and dysfunctional coagulopathy. Drug-induced intracerebral haemorrhages are related to anticoagulant thrombolytics, sympathomimetics, methamphetamines or cocaine (1, 7). Cases of intracerebral hemorrhages in relation to sildenafil use are being increasingly reported recently (1, 3, 4, 7, 11).

Sildenafil is a selective phosphodiesterase-5 (PDE-5) enzyme inhibitor. With the inhibition of PDE-5, the amount of cyclic-guanosine monophosphate (cGMP) in the vascular smooth muscle cells in the corpus cavernosum increases, leading to a relaxation of muscles and vasodilatation (1). Studies have shown that the NO-c-GMP pathway leads to cerebral vasodilatation with a similar mechanism (1, 4). Alpsan et al. has shown that the effect of PDE-1 and PDE-2 on cerebral bleeding is affected by sildenafil. This increase in blood flow may increase the risk of intracranial haemorrhage (1).

The side effects of sildenafil are well known. There are side effects related to vascular structures such as headache, flushing, dizziness and nasal congestion (10).

Another result of the non-prescription use of the drug is usage in improper dose. The recommended starting dose of sildenafil should be 50 mg and the maximum dose within 24 hours should be 100 mg (10, 11).

Sildenafil is the best selling drug in the global market for the treatment of male impotence (7). In addition to the use of prescription sildenafil, the non-prescription use of the drug is significantly high due to the ease in access to the drug without a prescription.

In this study; an intracerebral hemorrhage case due to the ingestion of alcohol with sildenafil where surgical treatment was not possible is presented. Although there are cases of subarachnoid haemorrhage and intracerebral hemorrhage caused by the use of sildenafil, there are few cases in the literature reporting intracerebral or subarachnoid hemorrhage associated with the use of sildenafil (1, 7, 8, 11, 10).

Sildenafil is not reported to interact with ASA, antacids and alcohol (6). It is difficult to understand the effects of alcohol ingestion in cases of intracranial hemorrhage caused by the combined ingestion of sildenafil with alcohol. There are reports in literature that point to a possible relationship between the ingestion of alcohol and spontaneous intracerebral

APPENDIX N-3

hemorrhage (2, 6, 9). There is no data suggesting an increase in the risk of spontaneous intracerebral hemorrhage due to combined ingestion of alcohol and sildenafil. However, our spontaneous intracerebral hemorrhage case after ingestion of alcohol and sildenafil indicates that this could be a harmful combination.

CONCLUSION

Although there is inadequate data to connect intracerebral hemorrhage to the combined use of alcohol ingestion and non-prescription use of sildenafil, caution should be exercised about drinking alcoholic beverages when using sildenafil as this may increase the risk of spontaneous intracerebral hemorrhage.

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Intracranial aneurysm and sildenafil

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Sildenafil is one of the most commonly used drugs for the treatment of erectile dysfunction. To date, we found five reported cases of intracerebral bleeding and two reported cases of subarachnoid hemorrhage related to sildenafil use. We report a 49-year-old hypertensive and diabetic patient who presented with acute pulmonary edema and loss of consciousness following ingestion of 100 mg of sildenafil prior to sexual intercourse. He was not previously aware of the presence of an aneurysm and had no family history of it. Computed tomography of his head revealed a subarachnoid hemorrhage due to rupture of a saccular aneurysm with subsequent repeat hemorrhage within a few hours of presentation. A sudden increase in blood pressure led to pulmonary edema. Studies have shown that sildenafil acts on phosphodiesterase-1, -2 and -5 receptors and leads to a secondary increase in intracerebral circulation and vasodilatory effects, leading to sympathetic overactivity which increases the risk for intracranial bleeding.

Sildenafil, marketed as Viagra, is a widely used phosphodiesterase (PDE)-5 inhibitor to treat male sexual/erectile dysfunction and to increase libido and sexual performance. The common adverse effects of this drug include headache, flushing, indigestion, and impaired vision. Five cases of intracerebral bleeding and two cases of subarachnoid hemorrhage (SAH) due to sildenafil use have been reported (1–7). We report a 49-year-old man who presented with a hypertensive crisis and an SAH caused by rupture of a saccular intracranial aneurysm during sexual intercourse following sildenafil intake.

CASE REPORT

A 49-year-old man with diabetes mellitus and hypertension was brought in to the emergency department due to acute-onset shortness of breath and loss of consciousness during sexual intercourse. The patient had ingested 100 mg of sildenafil prior to the event (unknown time gap). Reportedly, he was diaphoretic and short of breath and required intubation due to a low Glasgow Coma Scale score of <7. His blood pressure was 181/105 mm Hg with a mean arterial pressure of 124 mm Hg. His chest examination revealed bibasilar crackles. A neurological examination was not completed because the patient was sedated. His pupils were round and reactive with normal deep tendon reflexes, and he could localize the pain. Routine blood counts, platelet

counts, and coagulation factors were normal. His chest x-ray revealed diffuse bilateral opacities consistent with pulmonary edema. An electrocardiogram showed a normal sinus rhythm. An arterial blood gas showed high anion gap (29) metabolic acidosis with respiratory acidosis: pH 7.22; partial pressure of oxygen, 68 mm Hg; partial pressure of carbon dioxide, 42.7 mm Hg; bicarbonate, 17.1 mEq/L; and lactate, 4.7 mmol/L. Bedside transthoracic echocardiography showed normal systolic function with no regional wall motion abnormality and grade II diastolic dysfunction.

Computed tomography of the head showed a massive acute SAH with the largest blood collection in the area of the anterior communicating artery with mild hydrocephalus (*Figure 1a*). The patient was started on mannitol 100 g over 30 minutes and underwent computed tomography angiogram of intracranial vessels, which showed an aneurysm at the junction of the right anterior cerebral artery and anterior communicating artery (*Figure 1b*). He was urgently taken to the operating room and underwent ventriculostomy. While in the operating room, his ventricular pressures increased, his pupils dilated, suggesting brain herniation, and he underwent bilateral decompressive craniotomy and aneurysm clipping. Postoperatively, his Glasgow Coma Scale score was 3/15, and he was cooled to maintain temperature around 35°C for 48 hours. Because of his low Glasgow Coma Scale score, his chances for safe extubation seemed unlikely, and a tracheostomy and percutaneous endoscopic gastrostomy tube were placed on postoperative day 8. On postoperative day 10, he started to improve slowly, and his Glasgow Coma Scale increased to 15/15 on postoperative day 31. He continued to require a tracheostomy collar and was discharged to a neurorehabilitation institute.

DISCUSSION

Sildenafil inhibits PDE-5-mediated hydrolysis of cyclic guanosine monophosphate (cGMP), leading to increased intracellular cGMP levels in the vascular smooth muscle of the corpus cavernosum and resulting in smooth muscle relaxation and arterial vasodilation (8). The amount of cGMP in

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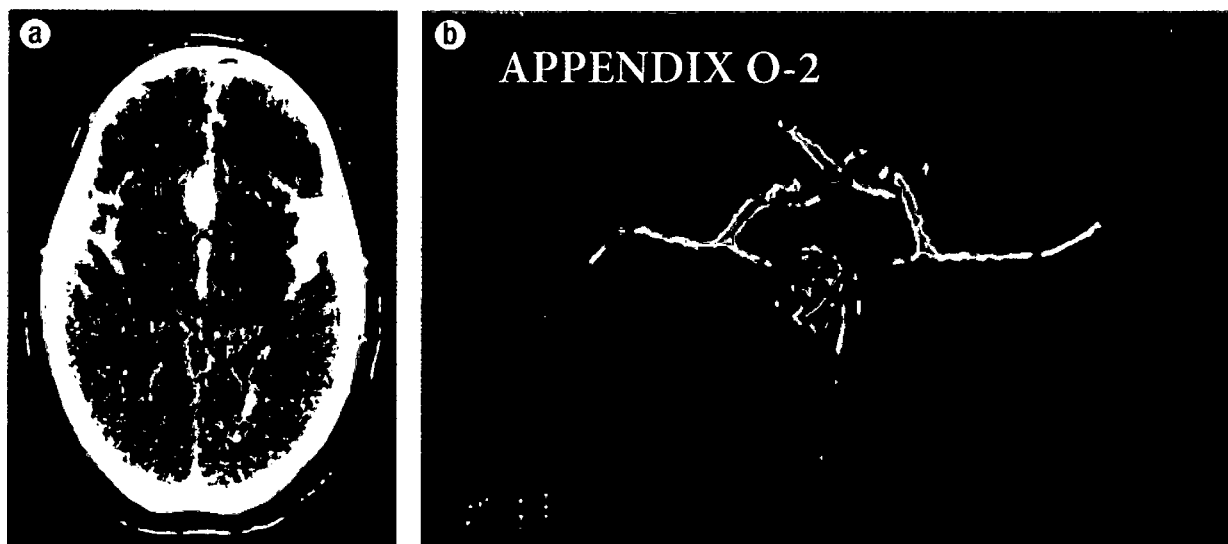


Figure 1. (a) Computed tomography demonstrating a subarachnoid hemorrhage. (b) Computed tomography angiography showing an anterior carotid artery aneurysm.

cerebrovascular smooth muscles is affected by nitric oxide and PDE. Nitric oxide activates guanylate cyclase in the cerebral arterial cells. The activated guanylate cyclase converts guanosine triphosphate to cGMP. The latter causes relaxation of vascular smooth muscle cells in the cerebral vasculature (9, 10).

The relationship between intracranial hemorrhage (ICH) and sildenafil use is likely due to increased blood flow to the intracranial vessels, which is significantly increased during sexual intercourse. Increased blood flow to the cerebral blood vessels facilitates rupture of the cerebrovascular vessels in patients with other hemorrhagic risk factors (3). Ballard et al suggested that sildenafil also acts on PDE-1 and PDE-2, which are involved in controlling cerebral circulation (11). Studies on mice have demonstrated that sildenafil decreases cerebral vasospasm by increasing and restoring cGMP levels (12). The reported adverse effects of sildenafil include headache, visual disturbances, pupil-sparing third nerve palsy, and transient hypertension, and these symptoms suggest that sildenafil also affects brain microvasculature regulation (13, 14). Unusual susceptibility to this drug could lead to abnormal vasodilatation of cerebral arteries and abnormal redistribution of arterial blood flow in the brain.

The hypothetical relationship between ICH and sildenafil ingestion is not well understood (2, 5). Transcranial Doppler

studies have shown that sildenafil increases cerebrovascular reactivity and causes vasodilation with increased blood flow and volume (15). The vasodilatory effect of sildenafil causes hypotension that could lead to an increase in sympathetic activity, which might be the reason for secondary hypertension leading to SAH, as occurred in our case. Ayberk et al reported a case of intracerebral bleed in a healthy 35-year-old man 3 hours after ingestion of 50 mg of sildenafil without any sexual activity (5). This supports our conclusion that sildenafil results in reactive sympathetic hyperactivity that leads to ICH regardless of the presence or absence of other risk factors, such as hypertension and sexual intercourse. Nevertheless, our known hypertensive patient had an elevated blood pressure and SAH after sildenafil use. Whether the hypertensive crisis in this patient caused by sildenafil was secondary to sympathetic hyperactivity or sexual intercourse or whether the ICH itself caused hypertension cannot be determined. Also, we do not know if there is a dose-related effect which causes ICH. All reported patients ingested 50 mg or more (Table 1).

Sildenafil citrate has been shown to be safe in patients without cardiovascular disease but is contraindicated in those with acute coronary syndromes, life-threatening coronary arrhythmias, and recent stroke. The US Food and Drug Administration advises

Table 1. Reported cases of subarachnoid hemorrhage after sildenafil use

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Our case
Age (years)	62	44	62	67	35	49	33	49
Hypertension	Yes	No	Yes	No	No	Unknown	No	Yes
Dose of sildenafil (mg)	50	4 tablets (unknown strength)	50	50	50	Unknown	50	100
Glasgow Coma Scale: admission and discharge	15/15 15/15	15/15/drowsy Deceased	15/15 15/15	15/15 15/15	12/15 15/15	Dead on arrival	3/15 Unknown	Low/intubated 15/15
Type of bleed	Thalamic and capsular	Left temporal	Right subthalamic	Left temporal subcortical	Caudate nucleus	Left ACA, SAH	Right basal ganglia, SAH	Right ACA, SAH

ACA indicates anterior cerebral artery; SAH, subarachnoid hemorrhage. Cases appear in references 1–7.

cautioned use of sildenafil in patients with a history of myocardial infarction or stroke within 6 months and those with resting hypotension, severe hypertension (<170/110 mm Hg), and heart failure (16).

All five previously reported intracerebral hemorrhages with sildenafil use presented with minimal volume hemorrhage in elderly patients with a risk factor of ICH, and surgical evacuation was not required (Table 1) (1–5). However, the previous two reports of SAH with sildenafil use were associated with severe bleeding (6, 7). One patient required emergency decompression due to impending herniation, and the other patient was pronounced dead on arrival (6, 7). Our patient rebled following the initial SAH and underwent ventriculostomy and bilateral decompressive craniotomy. His neurological status improved tremendously, and his Glasgow Coma Scale score was 15/15 on discharge. In conclusion, sildenafil is a relatively safe and widely used medication to treat erectile dysfunction. However, serious complications, such as severe ICH and SAH, have been reported with its use.

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Case Studies

Acute Intracranial and Spinal Subdural Hematoma Associated with Vardenafil

Takaaki Nakamura, MD, Genya Watanabe, MD, Ryuhei Harada, MD,
Emiko Kawasaki, MD, PhD, Kenichi Tsukita, MD, and Yasushi Suzuki, MD, PhD

A 28-year-old healthy man was admitted to our hospital because of right-sided headache, vomiting, and lower back pain after the administration of vardenafil. Computed tomography and magnetic resonance imaging of the brain showed a small, right-sided, subdural hematoma. A lumbar magnetic resonance imaging showed a longitudinally extended subdural hematoma. He had no history of trauma. We speculated that vardenafil might have had an association with the bleeding. Several reports have suggested a relationship between phosphodiesterase-5 inhibitors and intracerebral or subarachnoid hemorrhage. Our case suggested that there may also be risks of bleeding into the subdural space. Although headache and nausea are common side effects of vardenafil, hemorrhagic diseases should also be considered when symptoms are severe or prolonged. **Key Words:** Subdural hematoma—vardenafil—phosphodiesterase-5 inhibitor—spine.

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Introduction

Phosphodiesterase (PDE)-5 inhibitors, such as vardenafil, are widely used for the treatment of erectile dysfunction. Headache and vomiting are common side effects of PDE-5 inhibitors. Recently, cases of intracerebral and subarachnoid hemorrhages possibly representing the risks and severe adverse effects of PDE-5 inhibitors have been reported.¹⁻⁴ We report the case of a healthy young man with intracranial and lumbar, nontraumatic, acute sub-

dural hematoma (ASDH) associated with vardenafil ingestion.

Case Report

A 28-year-old man with no medical history, was admitted after a 3-day history of sudden-onset, right-sided headache with vomiting occurring 2 hours after taking 10 mg of vardenafil. He also noticed lower back pain after the headache onset. He had no history of trauma and his only cardiovascular risk was a 7-year smoking history. He reported having ingested vardenafil solely out of curiosity and denied sexual intercourse. His neurological examination result was nonfocal. Laboratory findings, including platelet count and coagulation panels, were normal. Computed tomography and magnetic resonance imaging (MRI) of the brain revealed a small, right-sided, subdural hematoma (Fig 1, A,B). Magnetic resonance angiography and venography showed no vascular lesions. Lumbar MRI revealed a longitudinally extended subdural hematoma (Fig 1, C,D). His symptoms gradually

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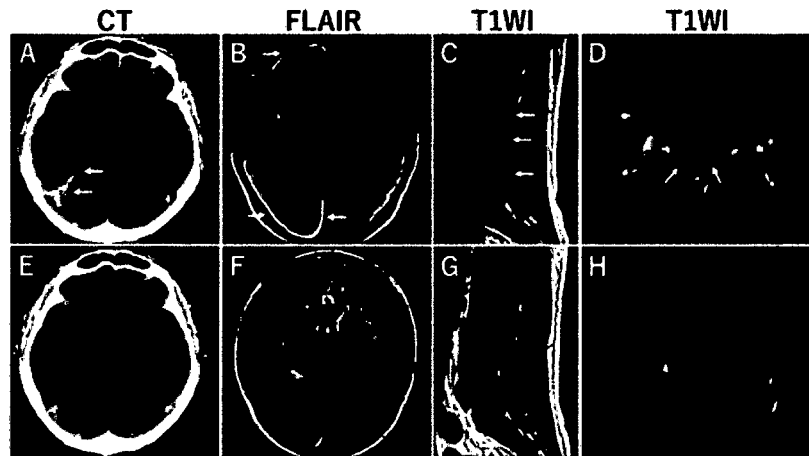


Figure 1. CT and MRI of the brain in the acute phase and after 1 month. (A) Axial CT views on day 3 demonstrate a right-sided, subdural hematoma along the tentorium cerebelli (arrows). (B) Axial view of FLAIR on day 5 shows a small, right-sided subdural hematoma (arrows). (C and D) Axial and sagittal views of the T1WI on day 10 show a longitudinally extended subdural hematoma (arrows). (E and F) CT and MRI of the brain after 1 month show a decrease in the size of the intracranial subdural hematoma. (G and H) Lumbar MRI after 1 month demonstrates disappearance of the spinal subdural hematoma. Abbreviations: CT, computed tomography; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; T1WI, T1-weighted image.

improved with conservative management, and all symptoms had completely disappeared 10 days after onset. Repeat computed tomography and MRI scans showed decreased intracranial and spinal hematoma sizes (Fig 1, E-H).

Discussion

To our knowledge, this is the first case of subdural hemorrhage associated with PDE-5 inhibitors. Concomitant intracranial and spinal ASDH are also rare phenomena.⁵ A previous study reported a 3% incidence rate for intracranial, nontraumatic ASDH,⁶ with risk factors including hypertension, vascular abnormalities such as aneurysm, and anticoagulation therapy.⁷ In contrast, similar to other reported cases, our patient had almost no risk factors.²⁻⁴ Although the underlying mechanism remains unknown, the vasodilatory and antiplatelet effects of PDE-5 inhibitors^{8,9} may be associated with the ASDH in our patient. Further evidence of the relationship between vardenafil and bleeding in our patient is based on the time from drug ingestion to headache onset, which corresponds to the time to maximum concentration of vardenafil.¹⁰ PDE-5 inhibitors may be associated with intracranial and spinal hematoma risks. When headache, vomiting, and lower back pain appear after the administration of PDE-5 inhibitors, the possibility of hemorrhagic diseases must be considered.

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A Case of Recurrent Lobar Intracerebral Hemorrhage in the Setting of Phosphodiesterase-5 Inhibitor Use

by Scott A. Lucchese, MD, Arshdeep S. Dhaliwal, MD, Arpanjeet Kaur, MD & Laura Qi, MD

This case bolsters existing evidence that phosphodiesterase-5 inhibitors as a class should be viewed with caution. As of publication, FDA warns against possible cardiovascular adverse reactions, hearing loss, hypotension, and priapism, however does not warn that intracerebral hemorrhage may be possible side effect.



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Abstract

Intracerebral hemorrhage occurs when a diseased blood vessel within the brain bursts. We present a case of 69-year-old patient with two sequential episodes of lobar intracerebral hemorrhage occurring during sexual intercourse. Both episodes were associated with the use of phosphodiesterase-5 inhibitors. This is the first case reported which is temporally associated with isolated bilateral lobar bleeds with appropriate use of phosphodiesterase-5 inhibitor on two different occasions associated with sexual intercourse.

Introduction

Intracerebral hemorrhage (ICH) (code 431, International Classification of Diseases, 9th Revision) is a neurological deficit documented by brain CT or MRI showing the presence of an intracranial bleed in the parenchyma of the brain.¹ ICH is a serious cerebrovascular condition associated with high mortality and morbidity in adults. Etiological factors for spontaneous ICH include vasculopathies, such as, cerebral amyloid angiopathy, hypertension, aneurysms, vascular malformations;

alcohol ingestion; coagulopathies; drugs; tumors; and genetics.²⁻⁴ The risk of lobar ICH significantly increases with age, as well.⁵

Oral phosphodiesterase-5 inhibitors are commonly used for the treatment of erectile dysfunction (ED). These medications are also thought to be possibly beneficial for treatment of cerebrovascular and pulmonary diseases. Sildenafil, a phosphodiesterase-5 inhibitor, has an expanding role in the treatment of pulmonary hypertension.⁶ Common side effects include flushing, headache, nasal congestion, changes in pulmonary blood flow and ischemic manifestations, such as transient ischemic attack, ischemic stroke, cerebral infarction, or ischemic optic neuropathy. Since the approval of these medications in 1998, multiple reports have tied their use, both appropriate and inappropriate, to ICH and retinal hemorrhages.^{2,7-20}

We present a 69-year-old male with clinical and radiological evidence of two (right and left frontal) incidences of lobar ICH occurring on two separate occasions during sexual intercourse, both associated with appropriate use of phosphodiesterase-5 (PDE-5) inhibitor for erectile dysfunction.

Case Report: History and Clinical Findings

The patient was a 69-year-old white male who experienced two episodes of intracranial lobar hemorrhage temporally associated with PDE-5 use. He had previous history of intracerebral hemorrhage nine months prior to presentation, coronary artery disease, colon cancer status post two resections, and subsequent chemo and radiation therapy, erectile dysfunction and hyperlipidemia. He presented to the emergency department with complaints of one-day history of headache, confusion, and inability to concentrate. The headache was bifrontal in location without radiation, 5/10 in intensity and squeezing in character. There was no associated photophobia, phonophobia, nausea, congestion or lacrimation. There was no slurring of speech, hearing loss, neck stiffness or significant weakness. The patient has been normotensive and non-diabetic throughout his life. He was on multi-vitamin, 81 mg aspirin, sildenafil (25mg) for his erectile dysfunction, and tamsulosin for benign prostatic hyperplasia.

He had strong family history of coronary artery disease and myocardial infarction. He had a daughter with brain aneurysm which was treated surgically. He did not smoke, drink, or use illicit drugs. His labs were within normal range without abnormal platelet count or INR.

On examination, he was well nourished and in no acute distress. The remainder of the general examination was unremarkable. On mental status exam he scored 12/30 on MMSE with deficits in all spheres except repetition and orientation to place. His executive functions were compromised with difficulty calculating and was also not able to follow three step commands. He was not able to repeat three objects consecutively and follow written commands. In addition, he had verbal and action perseveration. The remainder of the cranial nerve exam was unremarkable.

Motor exam was unremarkable. Deep tendon reflexes were symmetric. Sensation to all modalities was intact. He had no ataxia. Cortical sensations including graphesthesia and stereognosis were normal.

On fundoscopic exam, the patient had bilateral papilledema. The patient was hypertensive (160/90mmHg) and required intravenous (IV) hydralazine for control of blood pressure. While in the emergency department his headache resolved a few hours after presentation. He was started in emergency department on phenytoin for seizure prophylaxis after ICH.

Non-contrast computed tomography (CT) of brain showed acute left frontal lobe bleed and chronic right frontal encephalomalacia from prior ICH (Figure 1). About nine months prior to current presentation, he had presented with a similar syndrome and brain CT at that time showed large right frontal bleed (Figure 2—the remnant of this bleed is the source of chronic changes in Figure 1). Head Magnetic Resonance Imaging (MRI) exam showed a left frontal intracerebral hemorrhage with both a subacute and acute component with minimal mass effect on left lateral ventricle and no midline shift. The MRI was also notable for evidence of previous right frontal hemorrhage, mostly resolved, with resultant encephalomalacia. Periventricular T2 hyperintense signals were present in the frontal areas suggesting chronic small vessel disease (SVD) (see Figure 3 current bleed, Figure 4 for prior right bleed). Carotid duplex ultrasound demonstrated mild carotid plaques bilaterally without any significant stenosis. MRA angiogram of head and neck were negative for any aneurysm, arteriovenous malformations or other vascular anomalies.

On further discussion with the patient's wife on the second day of the admission, she noted that the patient's headache began while they were engaged in sexual intercourse. She also noted they had been engaged in intercourse leading up to the previous episode of ICH approximately nine months prior when the patient had the initial right sided frontal intralobar hemorrhage (Figure 4). She noted the prior headache occurred during intercourse while using tadalafil for erectile dysfunction. She also noted he had taken sildenafil (25mg) and was engaged in intercourse just prior to development of the headache which led to the current presentation, and discovery of the new left intralobar frontal hemorrhage (Figure 3).

The temporal relationship of the two occurrences of ICH on two different occasions with the use of the PDE-5 inhibitors was concerning for possible causality. It seems likely that type PDE-5 inhibitor use and sexual activity in the setting of underlying vascular pathology, possibly amyloid angiopathy, contributed to the bleeds. He had used PDE-5 inhibitors several other times in the past, but not with a great deal of frequency. The wife could not give a detailed history of this and the patient wasn't aware at that point and time how often he had used them. He never reported a sexual headache prior to his first presentation of ICH. He was counseled to stop taking any



Figure 1. Computed tomography of brain showing second episode of left frontal bleed and right frontal encephalomalacia from the first episode.

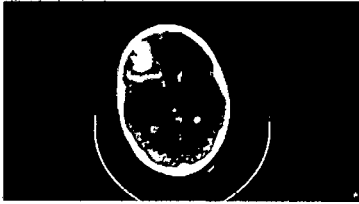


Figure 2. Computed tomography of brain showing first episode of large right frontal bleed.



Figure 3. FLAIR image with second episode of acute bleed in left frontal lobe and sequela of prior bleed with gliosis in right frontal region.



Figure 4. First episode of right acute frontal bleed with edema and mild midline shift; diffuse T2 signal hyper-intensity in the periventricular region consistent with small vessel disease.

PDE-5 inhibitors after his second episode. Unfortunately, he was not advised to discontinue use of PDE-5 inhibitors after his first episode of intracerebral hemorrhage.

The patient did well initially with conservative management after both bleeds. His phenytoin was discontinued at discharge. Approximately eighteen months after the second bleed, he developed partial complex epilepsy and was treated with levetiracetam which he tolerated very well. He had to give up his real estate business due to his executive dysfunction resulting from the bilateral bleeds.

Discussion

The overall incidence of intracerebral hemorrhage (ICH) is 12 to 15 cases per 100,000 individuals or about 40,000 cases per year in the United States. Spontaneous (atraumatic) primary ICH is a catastrophic form of stroke associated with high morbidity and mortality

and a substantial recurrence risk. Lobar ICH location is associated with the risk of subsequent ICH recurrence, likely because of the type and severity of the underlying small vessel diseases (microangiopathies), which include arteriolosclerosis, lipohyalinosis, and cerebral amyloid angiopathy (CAA).¹⁸

Intracerebral hemorrhage mortality is about 40% at 30 days, similar to SAH in acute mortality.¹ The five-year mortality rate is over 50% (52% for males, 56% for females) in ICH patients older than 45 years, and the 10-year survival rate is 24.1%.^{1,11} For those who survive a spontaneous ICH, the risk of recurrence is in the 2% range, annually.¹ Since our patient was normotensive and non-diabetic, it is highly suspicious that amyloid deposition might have played a significant role in altering the microstructure of the cerebral vessels.

Fourteen cases of adult intracranial hemorrhage associated with the use of PDE-5 were found on review of the English language literature. The case reports' subjects range from 33 years old to 70 years old. All developed cerebral hemorrhage symptoms (including headache, dizziness, blurry vision, decreased mentation, and nausea) 30 minutes to three hours after ingestion of PDE-5 inhibitor. None of these subjects had history of ICH. One report noted the patient described was found to have an arterial venous malformation, which was thought to be the causes of the hemorrhage.²⁶ None of the other cases reported known vascular malformations. Bleed location varied from cortical to subcortical without any appreciable correlation to age of subjects. Dosage varied from appropriate to excessive, but it remains unclear what the degree of dose related risk of ICH is associated with PDE-5 use.^{1,7-10,12,13,15,17-19,21-24, 25}

The relationship between ICH and PDE-5 inhibitors is likely due to increased blood flow to the intracranial vessels during sexual intercourse which is further enhanced by concurrent use of these drugs. Sexual intercourse is known to produce a hyper dynamic circulatory state in both men and women, manifested by increased heart rate and blood pressure.^{7,15} Following sexual stimulation, penile erection occurs through the release of nitric oxide (NO), which causes dilation of the blood vessels of the corpus cavernosum via an accumulation of cyclic guanosine monophosphate (cGMP). The PDE-5 inhibitors enhance this vasodilatory effect of NO-cGMP pathway by inhibiting PDE-5, the enzyme responsible for breakdown of cGMP. Studies have

also shown that sildenafil acts on phosphodiesterase-1, -2 and -5 receptors and leads to a secondary increase in intracerebral circulation and vasodilatory effects, leading to sympathetic over activity which increases the risk for intracranial bleeding.^{25,26} Side effects of sildenafil, including flushing, headache, nasal congestion, and changes in pulmonary blood flow indicate the multisystem vasodilation caused by these drugs.^{27,28}

Our case appears to be first one highlighting the temporal relationship between usage of two separate PDE-5 inhibitors and two separate episodes of ICH in different areas of the brain in one patient. This case bolsters existing evidence that PDE-5 inhibitors as a class should be viewed with caution. As of publication, FDA warns against possible cardiovascular adverse reactions, hearing loss, hypotension, and priapism, however does not warn that ICH may be possible side effect.

Conclusion

This case of recurrent lobar hemorrhages revolves around use of PDE-5 inhibitors and ICH likely associated with preexisting microvasculature pathology, precipitating ICH. It illustrates the risk of intracranial hemorrhage associated with the use of PDE-5 inhibitors during sexual intercourse. It would appear to be a particularly cautionary tale in the instance of prior intracranial bleed, or in the setting of known cerebrovascular disease. It is of utmost importance to discuss the risks and benefits before prescribing such medications to patients with possible underlying vasculopathies and/or prior bleed. If it is desirable to use these medications, it is likely prudent to start at the lowest possible dose in these populations.

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Disclosure

None reported.

MM



CASE REPORT

Intracranial Hemorrhage Associated with Sildenafil Use: A Very Rare Complication

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Abstract

Intracerebral hemorrhage (ICH) (International Classification of Diseases, 9th Revision) is a neurological deficit documented by brain CT or MRI showing the presence of an intracranial bleed in the parenchyma of the brain. ICH is a serious cerebrovascular condition associated with high mortality and morbidity in adults. It can be classified as primary and secondary according to etiology. Primary intracranial hemorrhage often develops due to hypertension or amyloid angiopathy. Secondary intracranial hemorrhage causes are often tumor, aneurysm and vascular anomalies. Trauma is the most common reason of secondary ICH. Sildenafil citrate is a potent vasodilator agent used in the treatment of erectile dysfunction. Among its side effects, intracranial hemorrhage is a very rare complication. We present a case of a 54-year-old patient who was brought to the emergency department due to nausea, vomiting and confusion after the use of sildenafil. The patient was diagnosed with intracranial hemorrhage in the setting of sildenafil use after excluding other causes.

Keywords

Sildenafil citrate, Intracranial Hemorrhage, Nitric Oxide

Introduction

Sildenafil citrate is the first effective orally used drug for the treatment of erectile dysfunction (ED). Penis erection occurs with increased blood flow as a result of smooth muscle relaxation in the corpus cavernosum sinusoids. Nitric oxide released by sexual stimulation increases guanylate cyclase activation and causes synthesis of cyclic guanosine monophosphate (cGMP). cGMP provides smooth muscle relaxation, resulting in increased arterial flow and corporal veno-occlusion. Intracellular cGMP is destroyed by phosphodiesterase

enzymes. Although four phosphodiesterase isoforms (type 2,3,4,5) are detected in human penile tissue, the predominant isoform in this tissue is type 5. Sildenafil is an oral, potent and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5). Sildenafil increases the cGMP concentration in corporeal smooth muscles with this effect and strengthens the relaxant effect of nitric oxide. Sildenafil is 10-10,000 times more selective on PDE 5 than other phosphodiesterase isoforms. Numerous side effects of sildenafil have been reported since its use. On the contrary, in the literature, intracranial hemorrhage associated with sildenafil use is extremely rare. We wanted to present a patient with intracranial hemorrhage in life-threatening anatomical localizations in the setting of sildenafil use. This patient had no risk factors for intracranial hemorrhage.

Case Report

A 54-year-old male patient was admitted to the emergency department due to a loss of consciousness. According to the anamnesis taken from his wife, about 3-4 hours earlier, dizziness, nausea and vomiting started suddenly while chatting with her. Then the patient developed confusion and had difficulty understanding what others are saying. Finally, he was brought to the emergency department after the patient lost consciousness. According to information received from his wife, he received 2 sildenafil tablets (100 mg) 3 hours before the complaints started, to attempt sexual intercourse, but he could not. It was learned that there was no history of sildenafil use previously but he had an erection problem recently and it was prescribed by the urologist, to whom he applied on the recommendation of his wife.



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The patient had been normotensive and non-diabetic throughout his life. He had no hyperlipidemia. There was no drug use. He did not smoke, drink, or use illicit drugs. There was no drug addiction in the story taken from his family (cocaine etc.). His height was 1.77 meters and his weight was 81 kg. He had no family history of cerebral arteriovenous malformation, cerebral aneurysm or intracranial hemorrhage. The neurological examination at presentation was as follows: Blood pressure was 130/85, heart rate was 104 and his fever was 37.1. The patient was confused, extension response to pain and making incomprehensible sounds. The Glasgow Coma Score was 6. Direct and indirect pupillary light reflexes were absent and he had small pupils, which are both ~1.5 mm bilaterally. There is no eye deviation. No asymmetry was observed in muscle strength and tonus examination. Reflexes are 2+ and symmetric at the biceps, triceps, knees, and ankles. There is no response to plantar reflex bilaterally. His breath sounds were bilaterally rough in auscultation. There was no significant feature in laboratory tests. Platelet count and coagulation factors were normal. Urine toxicological examination was not performed. Afterward, the patient developed respiratory distress in the emergency department and he was intubated. Then he was transferred to the neurology intensive care unit. Cranial computed tomography (CT) scan revealed a hyperdense hematoma area

with vasogenic edema was detected. It was determined that the hematoma started from basal ganglia level and spread to mesencephalon and pons level inferior and to the 4th ventricle and pontocerebellar level in the posterior (Figure 1).

ICH secondary to sildenafil is a diagnosis of exclusion. The cranial CT angiography did not reveal any vascular anomalies or other reasons explaining the cause of ICH. In the medical history, we learned that the patient had no family history of cerebral arteriovenous malformation, cerebral aneurysm or intracranial hemorrhage.

Mannitol was started as an antiedema treatment. The patient developed acute renal failure on the 5th day of hospitalization and he was consulted to the nephrology department. Mannitol stopped and he was started receiving dialysis. Although inotropic support was started for the patient whose blood pressure decreased on the 12th day of his hospitalization, the patient died. We suggested an autopsy to clarify the etiology, but the relatives did not accept.

Discussion

Sildenafil citrate is the first effective orally used drug for the treatment of erectile dysfunction (ED). It improves impaired erectile function by increasing blood

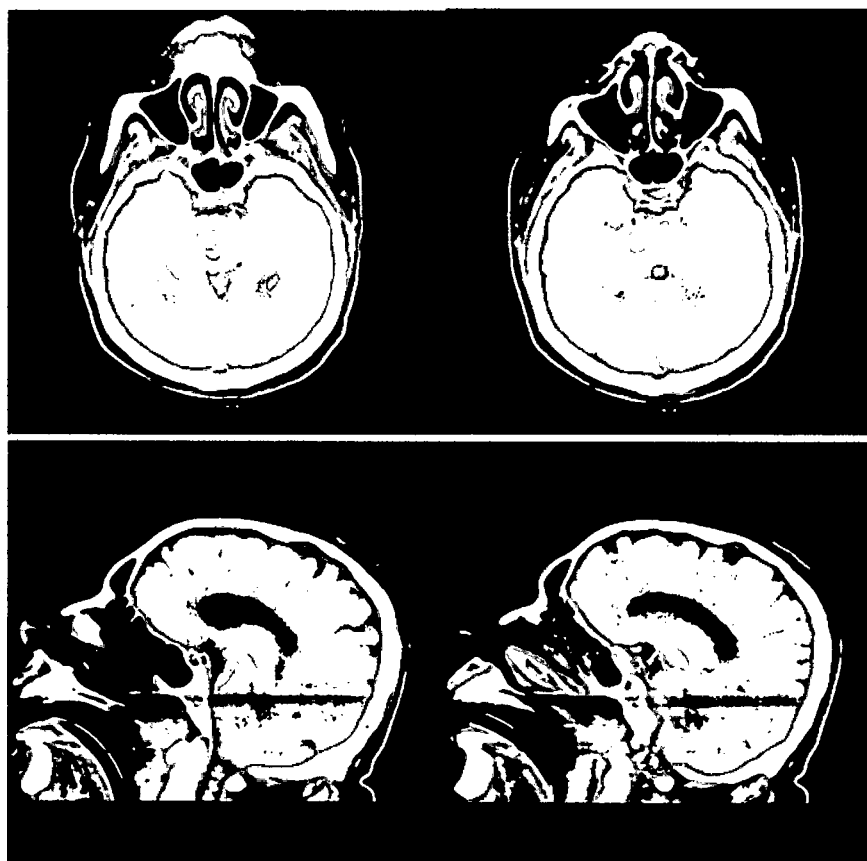


Figure 1: Computed tomography (CT) scan and lateral section of cranium for hyperdense hematoma area with vasogenic edema.

flow to the penis as a result of a natural response to sexual stimulation. The physiological mechanism that provides the erection of the penis requires the release of nitric oxide (NO) from the corpus cavernosum during sexual stimulation. Sildenafil does not have a direct relaxant effect on the isolated human corpus cavernosum, but it has the potential to increase the relaxant effect of nitric oxide present on this tissue. As with sexual stimulation, when the NO/cGMP pathway is activated, sildenafil inhibits the PDE5 enzyme, causing an increase in cGMP levels in the corpus cavernosum. Sildenafil increases the cGMP concentration in corporeal smooth muscles with this effect and strengthens the relaxant effect of nitric oxide. The NO - cGMP pathway may also be responsible for vasodilation in the brain through similar mechanisms [1]. PDE-1 and PDE-2 enzymes are involved in cerebral vascularity and sildenafil is also suggested to affect these enzymes [2]. Sildenafil has many side effects shown in the literature. The most common side effects are headaches, flushing and nasal congestion caused by vasodilation. Dyspepsia, respiratory infection, dizziness and visual and retinal disturbances are other side effects that can be observed. Changes in pulmonary blood flow indicates the presence of a systemic vasodilation induced by this drug [3,4].

Spontaneous (atraumatic) primary ICH is a destructive form of stroke associated with high morbidity and mortality. Intracerebral hemorrhage mortality is about 40% in the first 30 days, and this aspect is similar to subarachnoid hemorrhage in the acute period [5].

Blood flow to the brain vessels increases during sexual intercourse. Sildenafil also increases blood flow to brain vessels, the relationship between sildenafil and intracranial bleeding can be established in this way. It is known that sexual intercourse creates a hyperdynamic circulation state in both men and women due to increased heart rate and blood pressure [6,7]. It is also known that sildenafil acts on phosphodiesterase-1, -2 and -5 receptors. This act leads to a secondary increase in intracerebral circulation and vasodilator effects and ultimately leads to sympathetic overactivity, which increases the risk of intracranial bleeding [8,9].

About fourteen cases of adult intracranial hemorrhage associated with the use of PDE-5 were found on review of the English language literature. Cases were between 33 and 70-years-old and our patient was 54-years-old. All these subjects developed cerebral hemorrhage symptoms (including headache, dizziness, blurry vision, decreased mentation, and nausea) and our patient was admitted to the emergency department in a confusional state. In the literature in cases of intracranial bleeding with the use of PDE inhibitors, the onset of symptoms was observed within 30 minutes to 3 hours with drug intake. In our case, there was a history of 100 mg sildenafil use 3 hours before the emergency application. In the English literature, none of 14 cases

who developed intracranial hemorrhage due to PDE-5 inhibitor use, had a history of intracranial bleeding. The presence of arteriovenous malformation was detected in only one patient, and it was thought that it may be the cause of intracranial hemorrhage. There were no vascular malformations in other reported cases. Bleeding localizations varied considerably from cortex to subcortical areas, and no relationship was found with the age of those cases. The drug doses used by the cases varied between the normal range and overdoses and the relationship between dose and intracranial hemorrhage remains uncertain [10].

Conclusion

Consequently, high-dose sildenafil use may increase the risk of intracranial bleeding during sexual intercourse by causing cerebral vasodilation, although its relationship with the dose has not been clearly demonstrated. In the previous literature, we did not find any relationship between drug dose (25 mg, 50 mg, 100 mg) and intracranial hemorrhage. However, all subjects used doses of 50 mg or more once or twice in a short period of time. There may be an individual, unknown sensitivity to the drug. Probably, the mode of drug action in large part, may be not cumulative but idiosyncratic. It is extremely important to discuss the risks and benefits before prescribing such drugs to patients with possible underlying vasculopathy and/or previous bleeding. If it is necessary to use these drugs, it may be safer to use them in the lowest possible doses.

Conflict of Interest

None declared.

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