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Should Patients be Given an Initial Low Test Dose of Sildenafil?

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Abstract

Sildenafil is highly effective for treating erectile dysfunction (ED). However, its use has been associated with serious adverse events including myocardial infarctions and strokes, and 130 verifiable plus 112 unverified deaths reported to the US Food and Drug Administration during the 8 months after sildenafil was introduced in the US, and 522 reported deaths during the 13.5 months after its introduction. Moreover, some events have occurred in men taking their first dose of the agent, suggesting that sildenafil, like some drugs that affect blood pressure, may provoke a first-dose reaction. This possibility warrants extra caution to be used when initiating treatment with sildenafil. Such caution is not currently provided by the current dosage guidelines that, for example, recommend the use of sildenafil 50mg initially for most men between the ages of 18 and 65 years, despite wide differences in bodyweight, age, drug metabolism, health status and usage of other medications.

It can be difficult to identify the patient who may be unusually sensitive to the effects of sildenafil. Exercise stress tests have been recommended, but serious adverse events have occurred in men with normal stress tests following the ingestion of sildenafil. Blood pressure monitoring following sildenafil administration will not prevent a serious adverse drug event already in progress. This article discusses the advantages and disadvantages of initiating treatment with a low test dose of sildenafil, performed at home or in the doctor's office. The advantages of this approach include: (i) identifying patients who are highly sensitive to the effects of sildenafil and who may need no higher dose; (ii) minimising adverse effects such as flushing and dizziness that often frighten patients and may affect adherence; (iii) avoidance of major adverse events; and (iv) reassuring patients with ED who remain wary about trying sildenafil therapy.

Sildenafil is a highly effective drug for treating erectile dysfunction (ED)[1-7] but its usage has been associated with serious and sometimes lethal events in patients.[8] At present it is unknown if the events seen are attributable to a hypotensive or other unidentified effect of sildenafil, to the physiological stress of sexual activity, or to coincidence. To date the US Food and Drug Administration (FDA) has not attributed any sildenafil-related deaths directly to the drug. Sildenafil is now undergoing longer term scrutiny. This article presents the most up-to-date data that are available on the serious and lethal events that have been associated with use of this agent and discusses the possible advantages and disadvantages of giving patients a low initial test dose of sildenafil.

1. Literature Analysed

This review has been based on an evaluation of the following information.

- Relevant articles, cases, letters, editorials and other published works on sildenafil listed by Medline.
- Unpublished information on sildenafil provided courtesy of Pfizer Pharmaceuticals Inc., New York, NY, US.
- The most recent (November 1998) FDA report on sildenafil.[8]
- Published articles and respected drug and pharmacology references on the issues of first-dose reactions, the accuracy of adverse drug event data and related topics.

2. What Safety Data are Available?

After sildenafil was introduced for general usage in the US in March 1998, 6 million prescriptions for the drug were written within the next 8 months. During this same period, the FDA received verifiable reports of 130 deaths in the US associated with sildenafil use.[8] This generated considerable debate in the US, in both the public and medical sectors, about the safety of sildenafil. Similar debate took place in other countries and at least one, Israel, banned the importation of sildenafil.[9]

Since the FDA's reports of November 1998, little further information has been available regarding deaths in patients prescribed sildenafil. However, Azarbal et al.[10] recently reviewed FDA reports from April 1998 to June 1999, and after eliminating duplicate reports, noted 1473 serious adverse events associated with sildenafil, including 522 deaths, 517 myocardial infarctions, 199 cerebrovascular accidents, 161 instances of arrhythmia and 271 cases of syncope/ hypotension.

3. Does Sildenafil Provoke First-Dose Reactions?

Of the case reports of sildenafil-associated adverse events published in the literature, most do not mention whether the adverse event occurred with the first or later doses and some do not mention dose at all. However, in 3 reports,[11-13] the adverse event was identified as having occurred after the first or second dose. In one of the reports a 65-year-old man without any history of cardiovascular disease developed an acute myocardial infarction shortly after he took his first does of sildenafil 50mg, but before he had attempted sexual activity.[11] In another of the reports, a 56-year-old man with pre-exisiting microvascular disease and a history of smoking developed a complete third nerve palsy following his second use of sildenafil 50mg.[12] The third report described a 70-year-old man with mild-to-moderate hypertension and hypercholesterolaemia who experienced a myocardial infarction 1.5 hours after talking sildenafil 25mg; 2 weeks before a stress test was normal, although he had been experiencing chest pain.[13]

The occurrence of adverse events in association with initial doses of sildenafil raises the question of whether sildenafil may cause first-dose reactions (i.e. an increased frequency or increased severity of adverse events with initial doses of sildenafil) in some patients. This is an important issue because antihypertensive agents and other drugs that, like sildenafil, affect blood pressure have been associated with first-dose reactions.[14-20] Although prerelease research with sildenafil involved several thousand patients, severe first-dose reactions occurring at an incidence of 1 per 10 000 or less would probably not have been detected.[21]

4. Assessing the Incidence of Serious Adverse Events with Sildenafil

The FDA disclosed in its November 1998 report that in addition to 130 verified deaths, another 112 unverifiable deaths had been excluded from its statistics.[8] Furthermore, the FDA has acknowledged that '. . . because of underreporting and uncertainty concerning the number of persons exposed to a drug, it is not possible to calculate a true incidence rate of a particular event for a specific drug'.[8] Thus, the actual number of deaths that have occurred in patients taking sildenafil is not really known.

Past experience with other drugs has shown that voluntary reports to the FDA represent only a frac-

tion of the true incidence of adverse effects. It has been estimated that less than 1 in 1000 serious adverse effects are reported to the FDA.[21] *Goodman and Gilman's The Pharmacological Basis of Therapeutics*,[22] a highly respected pharmacology textbook, states that, 'Most physicians feel that detecting adverse reactions is a professional obligation, but relatively few actually report such reactions'. A 1995 hospital study revealed that an incident report was submitted in only 6% of identified adverse effects.[23] The authors concluded that, 'voluntary reporting identified only a small fraction of ADEs [adverse drug effects]'. Thus, physicians should not assume that the number of reported sildenafil-associated deaths is an accurate representation of their occurrence. The actual incidence may be considerably higher. A true incidence will not be known until proper pharmacoepidemiological studies are conducted.

Table I. Possible advantages and disadvantages of test dosing with sildenafil

Potential advantages
1. Avoids first-dose reactions and may help identify patients who are unusually sensitive to the effects of sildenafil
2. Reduces the likelihood of minor adverse events that can frighten patients or their partners and disrupt treatment
3. Low dose therapy may be sufficient for some patients
4. The current recommended dosage guidelines are general, not absolute and obviously cannot be ideal for all patients
5. Provides a safer approach with at-risk patients
6. Addresses psychological concerns about sildenafil
7. Minimises the risk of potential drug interactions
8. Reduces the risks with untested, off-label uses of sildenafil
9. Offers a gradual approach: what is the hurry towards full doses of sildenafil?
10. Allows physicians to feel confident that they have employed the safest approach possible with this controversial drug
11. By discussing test dosing with patients, they become active and usually highly cooperative participants in treatment decisions
Potential disadvantages
1. Test dosing of sildenafil is unproven in formal studies
2. Ineffectiveness and possible patient dissatisfaction
3. Test dosing could lead to inappropriate usage

5. Difficulties with Assessing Causality

Are sildenafil-associated myocardial infarctions and deaths attributable to hypotensive or other unidentified effects of sildenafil, to the physiological stress of sexual activity or to mere coincidence (i.e. the expected number of deaths within a specific population during a specific period)? If other drugs were to come under the same scrutiny as sildenafil, would 6 million prescriptions of these drugs in a similar group of patients be associated with 130 treatment-associated deaths? There are no definitive data to provide answers to these questions. The manufacturer and the FDA published warnings about sildenafil use in patients with cardiovascular disease in November 1998,[8,24] but it is not known if these warnings have remedied the problem.

Moreover, the FDA has reported that in 34% of cases the deaths or onset of symptoms leading to death occurred within 4 to 5 hours of sildenafil use.[8] However, this statistic is misleading because in 61 of the reported deaths the temporal relationship was not reported to the FDA. Excluding these 61 cases and the 2 cases where death was related to homicide and drowning, in 44 (65.7%) of the remaining 67 cases, death or the onset of symptoms leading to death occurred within 4 to 5 hours of taking sildenafil.[8] Of these 44 cases, 27 (40.6%) cases involved men who had participated in sexual activity, and this was considered the most likely cause of the event. The remaining 17 men (25.1%) did not engage in sexual activity, which raises the possibility of some other causative process including sildenafil. Furthermore, some men who experienced a myocardial infarction or died following use of sildenafil had mild or moderate ED and had engaged in sexual activity without incident before sildenafil became available. These cases also raise suspicion about a possible aetiological role of sildenafil.

6. Difficulties in Identifying At-Risk Patients

Patients who may be at risk with sildenafil can sometimes be identified by looking at their medical status, previous problems with drugs that affect blood pressure or other factors. Among the 130 cases reported to the FDA, 68% (90 patients) had 1 or

more risk factors for a cardiovascular event (hypertension, hypercholesterolaemia, cigarette smoking, obesity or previous cardiac history), but 12 had no identifiable risk factors, and no information about risk factors was reported for 28 other patients.[8]

It has been suggested that exercise stress testing might identify some at-risk patients.[18,25] Sexual activity has been implicated in some sildenafil-associated deaths, and prior stress testing might have been helpful in identifying some of these patients. However, serious and lethal sildenafil-associated events have occurred in men without cardiovascular disorders or who did not engage in sexual activity.[8,11,13] It is questionable whether exercise stress testing would have been helpful in identifying these patients. Similarly, blood pressure monitoring following the initial dose of sildenafil has been suggested. While this method may be helpful in some patients, it will not prevent many of the adverse reactions already in progress.

Overall, assessing risk factors and performing exercise stress testing may identify some, but not all, of the men who may be vulnerable to serious adverse events associated with sildenafil use. If experience with patients with hypertension is any guide, it is difficult to predict which patients will develop hypotension or other cardiovascular-related adverse events in response to antihypertensive drugs.[26,27] The same may be true for sildenafil.

7. Advantages and Disadvantages of Using Test Doses of Sildenafil

Because of the unanswered questions about sildenafil-associated adverse events and the widely varying responses of patients to the effects of medications, test dosing may offer a safer alternative to the current standard dosage recommendations for initiating sildenafil treatment. The advantages and disadvantages of this proposal are discussed in the following sections and summarised in table I.

7.1 Advantages of Test Doses

7.1.1 Avoiding First-Dose Reactions and Identifying Patients Unusually Sensitive to the Effects of Sildenafil

Initiating treatment in a manner that allows patients to experience the effects of sildenafil without encountering adverse effects is helpful for establishing a cooperative, long term therapeutic relationship. However, identifying patients who are unusually sensitive to the effects of medications can be difficult.[27,28] In light of the recent data on sildenafil-associated deaths, reasonable precautions should be taken in initiating sildenafil treatment. Established principles of antihypertensive therapy provide a model for prescribing sildenafil. Physicians intentionally prescribe low initial doses of antihypertensive drugs to test patients' responses and avoid adverse effects that might cause adherence problems. It is understood that many patients will ultimately require higher doses, but by starting with a lower dosage and increasing gradually, fewer adverse effects are provoked and long term adherence is improved. Sildenafil therapy can be easily adapted to this model.

7.1.2 Avoiding 'Minor' Adverse Drug Reactions Improves Adherence

Although physicians may consider adverse effects such as flushing, headaches or dizziness to be minor, these adverse effects can be unpleasant and unnerving to patients, especially since many patients are aware of the possible association between sildenafil with myocardial infarction and death. Newspapers and magazines have carried stories about men stopping treatment with sildenafil because of intense adverse effects, particularly flushing. These adverse effects are dose-related and can be minimised by test dosing patients initially.

7.1.3 Low Dose Therapy May Be Sufficient for Some Patients

The standard initial dose of sildenafil for men aged 18 to 65 years is 50mg. However, studies show that some men achieve satisfactory erectile function with a dose of only 25mg.[1,2,4,7,29,30] In 1 study comparing 25, 50 and 100mg of sildenafil with placebo, the frequency of penetration was increased

by 60, 84, 100 and 5%, respectively, compared with baseline.[1] Maintenance of erection after penetration increased by 121, 133 and 130%, respectively, compared with baseline. The sildenafil package insert offers similar findings.[24]

The percentage of patients whose response is completely satisfactory to treatment with sildenafil 25mg may be relatively small but identifying them is important because their heightened response at 25mg may be indicative of an increased sensitivity to the effects of sildenafil. Indeed, the FDA report[8] indicates that 78% of the deaths that occurred in patients taking sildenafil occurred at the 50mg dose and 95% occurred at the 50 or 100mg dose, whereas only 5% occurred with 25mg. This discrepancy may perhaps be explained by the greater use of the 50mg dose, but it may also reflect a greater degree of risk.

7.1.4 Alternative to General Recommended Doses

The manufacturer's recommended initial dose of sildenafil for a 65-year-old man is 50mg.[14,24] For a 66-year-old man, the recommended dose is 25mg. One might wonder if some profound physiological shift occurs between the ages 65 and 66 years to explain this abrupt 50% reduction in dose. Is the 65-year-old more similar physiologically to an 18-year-old, both of whom get 50mg, than to a 66-year-old? This is not the case. Drug companies are required by regulatory authorities to provide broad general dosage guidelines, but they cannot provide guidelines for every distinct situation among the vast population of potential users. Past experience demonstrates that the manufacturer-recommended doses of drugs are not always the ideal doses.[21,31,32]

Individualisation of the dosage for purposes of safety and/or efficacy are not only the physician's prerogative but also his or her responsibility. Doctors are expected to exercise their clinical judgement when it comes to selecting a specific dose for a specific patient. Such judgement should include an appreciation of the limitations of dose demarcations offered by drug manufacturers, as well as an awareness of the wide variation in and the unpredictability of drug response between individuals. Such variation may explain why deaths in men as young as 29 years and as old as 87 years have been associated with sildenafil usage.[8]

7.1.5 Providing a Safer Approach with At-Risk Patients

The manufacturer's guidelines for treating at-risk patients with sildenafil are ambiguous. The US product information states that caution should be used when treating patients with cardiovascular disease, marked hypotension or hypertension or retinitis pigmentosa.[14,24] It is uncertain what caution means. Should sildenafil be withheld? If so, should these disorders be listed as contraindications? If not, which doses should be used? Currently, the package insert provides no guidelines. What about the millions of patients with ED who have hypertension, hypercholesterolaemia or obesity, or who smoke cigarettes, all of which the FDA lists as risk factors for sildenafil-associated deaths?[8] If these are risk factors, how should these people be treated? Neither the manufacturer nor the FDA have offered dosage guidelines.

If a physician elects to treat an at-risk patient, test dosing provides a safer alternative for assessing the patient's response to sildenafil than immediate full dosing.

7.1.6 Addressing Psychological Concerns Regarding Sildenafil

According to an advert produced by the manufacturer of sildenafil, more than 6 million men in the US have now been prescribed this agent, although the number who have continued with treatment is unknown. Stories published in newspapers and magazines have reported that many men who have not used sildenafil, or their partners, are concerned about using it. Test dosing could alleviate people's fears about sildenafil-related reactions more than any other approach. Even though the FDA has not attributed any sildenafil-related deaths directly to the drug, people remain sceptical. Attributing the deaths to risk factors such as mildly elevated cholesterol levels, hypertension, obesity and cigarette smoking, or to the sexual act that the sildenafil facilitated, is not credible to many patients and members of the medical community.

Reassuring patients that sildenafil is being initiated at a very low, perhaps suboptimal, dose allows patients to 'dip their toe in the pool', so to speak, before 'diving in'. By reducing patients' anxiety about their first dose, the possibility of anxiety symptoms being misinterpreted as adverse effects of sildenafil is also reduced. Moreover, addressing patients' anxieties may actually increase sildenafil use. Men or their partners who have been wary may now feel safer in using sildenafil therapy.

7.1.7 Minimising the Risk of Potential Drug Interactions

Because sildenafil is metabolised by cytochrome P450, 2C9 and 3A4 pathways, the manufacturer recommends a lower initial dose for patients taking erythromycin, ketoconazole, itraconazole or saquinavir. However, a lower initial dose is not specifically recommended for patients taking cimetidine or ritonavir, both of which alter sildenafil pharmacokinetics substantially. Whether competitive inhibition may occur with the many other medications metabolised by these pathways is not known, but reports of others suggest possible interactions with alprazolam, atorvastatin, clarithromycin, fluconazole, diltiazem, fluoxetine, nefazodone, nifedipine, omeprazole, phenobarbital, sertraline, verapamil, grapefruit juice and many others[33,34] that are not mentioned in the manufacturer's product information. Because the list of potential interactions is long and a study of sildenafil with each drug is unlikely, test dosing may provide an extra margin of safety in patients taking these medications. The report by Cheitlin et al.[33] also warned of possible enhanced hypotensive effects in patients taking 2 or more antihypertensive drugs, or 1 antihypertensive drug and another that may inhibit sildenafil metabolism. Substantiating this concern over unanticipated adverse drug interactions is a report by Hayashi et al.[35] They described the case of a 51-year-old man who had intermittent Wolfe-Parkinson-White syndrome, who was taking doxazosin and who developed severe hypotension, chest pain and an arrythmia after drinking 1500ml of beer and taking sildenafil 50mg.

7.1.8 Greater Safety with Off-Label Uses

Sildenafil is being used for some disorders that were not investigated by the manufacturer or reviewed by the FDA.[36-40] These include sexual dysfunctions in women, sexual dysfunctions caused by antidepressant drugs, and male partners of couples undergoing treatment for infertility.[36-40] With other drugs, off-label uses sometimes require lower doses than those for the approved uses.[41-43] Until studies are conducted on these new uses for sildenafil, the risk of inadvertent overmedication may be reduced by test dosing these patients.

7.1.9 Offers a Gradual Approach to Full Doses of Sildenafil

Impotence is not an acute condition. Impotence is a long term problem that usually involves long term treatment. Patients are usually very interested in initial test dosing if it is for the purpose of safety and if they know that subsequent doses will be titrated, if necessary.

7.1.10 Advantages for Physicians

Some physicians are satisfied that sildenafil-associated myocardial infarction and deaths are adequately explained by concomitant risk factors, the stress of sexual activity or coincidence. Nevertheless, it would be a thankless and probably fruitless task to try to tell this to the wife of a man with no cardiac history who developed a myocardial infarction shortly after taking sildenafil without even engaging in sexual activity, for example the first case described in section 3,[11] or if the man had participated in sexual activity prior to sildenafil without incident and now experienced a serious adverse event in association with sildenafil and sexual activity. It would equally be difficult to explain the case in which a man's exercise stress test was normal, yet he then experienced a myocardial infarction or died in close association with his first dose of sildenafil. Law suits have been filed in such cases, and statistical coincidence is not a particularly persuasive defence. Test dosing with a lower initial dose might reduce the occurrence of such incidents and would demonstrate that the physician had attempted to administer sildenafil in the safest possible manner.

1. Because it is sometimes difficult to predict those people who will be sensitive to the effects of sildenafil, we have agreed to start treatment at a low test dose. *The goal of the test dose is safety. Once we know that you can tolerate sildenafil at this dose, we can adjust the dose to obtain the best response.* The test dose may work well for you, but for most men it provides only a partial improvement in their erectile dysfunction, and for some others no improvement at all.

2. Please tell your partner that the purpose of the test dose is safety. Explain that there is no need to worry if this dose does not produce a complete response and that adjusting the dose usually solves this problem. Do not take a second dose of sildenafil on the same day you took the test dose.

3. On the day you are planning to try sildenafil for the first time, avoid taking other medications or using alcohol, if possible. If you are receiving daily medication, take it as far removed from taking sildenafil as possible.

4. **Instructions:** Take the sildenafil dose that we agreed upon. Relax. Occupy yourself and your partner with conversation, television, music, etc. The effect of sildenafil usually begins after 30 to 60 minutes, but it may take longer. If your response is satisfactory enough for you to initiate sexual activity, you can do so. The most common adverse effects are flushing, dizziness, headache, muscle tightness and a sensation of warmth. According to the manufacturer of sildenafil, these effects occur in about 30% of patients taking the standard doses. With the lower test dose, these adverse effects occur infrequently and, if they do occur, they are generally milder.

Fig. 1. Test dosing for sildenafil: suggested instructions for patients.

7.2 Disadvantages of Test Doses

7.2.1 Test Dosing is Untested and Unproven

To date, no studies that utilise test dosing have been conducted. However, experience with other groups of drugs such as antihypertensives and antidepressants has shown that lower initial doses that do not provoke adverse events may improve long term adherence.

7.2.2 Ineffectiveness and Patient Dissatisfaction

A test dose of 25mg will provide suboptimal treatment for most men aged 18 to 65 years. However, a few may obtain a satisfactory erection, others may still achieve successful intercourse and, in most patients, the drug will produce at least some response. For patients, these are signs that sildenafil will indeed work when titrated properly. Furthermore, if given the choice, patients often prefer to start at a lower dose for safety reasons.

7.2.3 Inappropriate Usage

If test dosing proves to be effective, some physicians may be tempted to prescribe sildenafil to patients who have contraindicated conditions but nevertheless request the drug. Such usage should be avoided until studies confirm the safety of any sildenafil dose in these situations.

8. Discussion

8.1 Practicality of Test Dosing with Sildenafil

Because the sildenafil tablet is unscored and irregularly shaped, a physician cannot simply prescribe 50mg tablets and instruct the patient to split one in half. However, pharmacists will split a sildenafil tablet at the physician's request. Some patients do so themselves with pill cutters as a way to reduce costs. Alternatively, doctors can write a prescription for 1 or two 25mg tablets and then approve a second prescription at 25 or 50mg depending on the patient's response. The cost for writing an extra prescription is about $US10 to 20 in the US, which many patients will probably be willingly to pay. For men aged 66 years or more the standard dose is 25mg, and half doses can also be obtained by tablet splitting. Doses as low as sildenafil 10mg are pharmacologically active.[2]

8.2 Who Should Decide Whether to Use Test Doses with Sildenafil?

Physicians are responsible for making dose decisions. However, the excellent effectiveness record of sildenafil together with its association with serious adverse events provides compelling reasons for involving patients in dose decisions. Ethically, it may be argued that doctors are obligated to inform patients about the safest methods of initiating drug therapies, even if these methods involve different (lower) doses than suggested by the manu-

facturer. After all, it is the patient's well-being that is at risk, not the physician's. Physicians are expected to provide informed advice but not necessarily to make unilateral decisions about dosage without the patient's knowledge and consent. Educated patients understand that there is a benefit/risk factor with any treatment decision, and they usually appreciate being involved in treatment decisions. In this author's experience, patients are much more receptive to strategies such as test dosing than are physicians. Doctors can save time and ensure patients' understanding of test dosing by providing a leaflet explaining the procedure. Such a leaflet is illustrated in figure 1.

9. Conclusions

Sildenafil has been shown to be an effective treatment for ED, but its use has been associated with 130 verified plus 112 unverified deaths reported to the FDA within 8 months following its introduction in March 1998,[8] and with 522 reported deaths within 13.5 months following its introduction.[10] Some of these deaths occurred in men with no risk factors and not engaging in sexual activity. Case reports suggest the possibility that sildenafil may cause first-dose reactions in some patients. Some experts have recommended exercise stress testing with some patients prior to sildenafil use, or blood pressure monitoring following the initial doses of sildenafil; however, the first method will not identify all at-risk patients and the second will not prevent adverse events already in progress. The use of an initial low test dose of sildenafil may help to identify patients who are unusually sensitive to the effects of sildenafil, prevent serious adverse events, prevent first-dose reactions, reassure patients who have anxiety about sildenafil and facilitate a smooth and successful inception of treatment. Initiating treatment at a low dose is an effective strategy with other types of medications and it can easily be applied with sildenafil. Test dosing can be done at home or at the doctor's office and it can be utilised following exercise stress testing or in conjunction with blood pressure monitoring to provide maximum safeguards. Patients should be involved in the decision whether to use test dosing with sildenafil. In addition, an updated report from the FDA would add a much needed perspective on current concerns about sildenafil and establish whether the steps taken by the FDA and the manufacturer in November 1998 have been effective in reducing the occurrence of sildenafil-related deaths.

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