

### Editorial Commentary

Rochira V, Granata ARM, Balestrieri A, Madeo B, Carani C. Effects of sildenafil on nocturnal penile tumescence and rigidity in normal men: randomized, placebo-controlled, crossover study. *J Androl.* 2002;23:566–571.

The ability of sildenafil to augment sexually stimulated penile erections is now well established. The duration of activity is somewhat unclear, and anecdotal reports have surfaced regarding prolonged or sustained activity.

In an effort to understand the actual duration of the effects of sildenafil on penile erection in normal men, the authors have decided to elegantly evaluate nocturnal penile tumescence erections and rigidity in a group of men with normal erectile activity. They use nocturnal penile tumescence monitoring to monitor sleep-related erections after taking either sildenafil or placebo.

The data show, quite interestingly, that in these normal individuals sildenafil did enhance nocturnal erectile activity. Sildenafil increased the total duration of rigidity, the total number of valid erections, and the maximum rigidity and maximum increase in tumescence and total duration of increase in penile circumference. The majority of these parameters were significantly increased after sildenafil. It is interesting that the effects were observed over the course of 4 hours, and in some individuals the effects were observed over the course of 8 hours.

These interesting data shed a great deal of light on the current anecdotal experience of many clinicians vis à vis the use of sildenafil. These data suggest that sildenafil has long-lasting effects on some individuals, perhaps up to 8 hours. These data explain why certain individuals may be able to take sildenafil at night and to use the morning

erection for intercourse. All in all, these data add significantly to the body of literature regarding sildenafil and the ability of a man's erectile function to improve over the course of several hours. These data also suggest that the erectile function remains improved over the course of the time evaluated herein, 4 hours or 8 hours.

The obvious downside of this finding is that now we have evidence to suggest that the effects of sildenafil may be longer lasting than was previously believed. The questions to ask include, what is the long-term effect of this on nonsexually stimulated erectile activity; what is the effect of this result on men with abnormal erectile activity; will this drug have any untoward effect on penile physiology with respect to nitric oxide or cyclic guanosine monophosphate production at the level of the penis; and should we be concerned about any other issues in light of these new data?

This study is very useful and offers great insight into the duration of sildenafil-mediated effects on sleep-induced erectile activity. However, it also raises new questions that will need to be addressed in future studies. The authors are to be congratulated for a novel design that sheds light and offers new and important information on the physiology of erections under the influence of sildenafil.

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### Response to Commentary

Rochira V, Granata ARM, Balestrieri A, Madeo B, Carani C. Effects of sildenafil on nocturnal penile tumescence and rigidity in normal men: randomized, placebo-controlled, crossover study. *J Androl.* 2002;23:566–571.

We thank Allen Seftel for his comments on the paper, "Effects of sildenafil on nocturnal penile tumescence and rigidity in normal men: randomized, placebo-controlled, crossover study." We take the opportunity to point out that in addition to the unanswered questions suggested by Dr Seftel, our work leaves still other unresolved issues.

Sildenafil improves sleep-related erections in men with (Montorsi et al, 2000) and without erectile dysfunction. Does this mean that sildenafil can also improve erections in normal men during sexual activity, and if it does, would use of sildenafil for this purpose be appropriate? Would use of sildenafil for this purpose lead to any neg-

ative effects? In clinical practice, keeping in mind that sleep-related erections are only slightly, if at all, affected by external factors, would nocturnal penile erection monitoring after sildenafil administration be useful in order to discriminate nonresponding from responding patients?

Our study suggests a prolonged efficacy of sildenafil, at least on nocturnal penile erections. In this view, future research could investigate the possible therapeutic effect of frequent sildenafil administration (eg, once or twice weekly before bedtime) on erectile dysfunction, even though sildenafil administration is not strictly linked to a following sexual activity.

Future studies could be helpful in developing new strategies for the use of sildenafil.

## From Androlog

*Note:* Postings to *Androlog* have been lightly edited for grammar and usage before publication.

In spite of the progress that in vitro technologies have generated in the management of severe male factor infertility, some clinical situations still pose challenging clinical dilemmas. One such circumstance is that of the male patient who is found to have sperm in the ejaculate but with 0% motility. Would testicular biopsy likely yield motile sperm in such a situation, and if not, would intracytoplasmic sperm injection (ICSI) be of use? Also, if ICSI is used, what is the best method for determining which sperm to inject? These questions were proposed to the members of *Androlog*. Let's see what advice was offered.

I submitted the following question regarding one of my patients:

Esteemed Colleagues: I am currently evaluating a 28-year-old gentleman whose semen analyses have shown excellent sperm counts on 2 occasions (99 and 102 million per mL, respectively) but 0% motility. He is completely normal on physical examination and has no correctable factors that I can identify. His past medical history is noncontributory. We have not, thus far, performed any additional tests to evaluate sperm viability. He and his wife are very interested in establishing a pregnancy and are willing to consider ICSI if this would be of help. I would be interested in the group's current thoughts on 2 questions: 1) How optimistic are you that hypo-osmotic swelling (HOS) (or other techniques) would reliably identify sperm suitable for ICSI in a case such as this? 2) Does anyone feel any optimism that testis biopsy might yield motile sperm, which could then be used in an ICSI procedure? Your thoughts on this would be much appreciated.

Randall B. Meacham, MD, Denver, Colorado

## References

- Montorsi F, Maga T, Strambi LF, Salonia A, Barbieri L, Scattoni V, Guazzoni G, Losa A, Rigatti P, Pizzini G. Sildenafil taken at bedtime significantly increases nocturnal erections: results of a placebo-controlled study. *Urology*. 2000;56:906-911.

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Dr Christopher De Jonge made the following excellent observations in response to Dr Meacham's questions about 100% nonmotile sperm:

1) How optimistic are you that HOS (or other techniques) would reliably identify sperm suitable for ICSI in a case such as this? I am very optimistic that if the plasma membrane is functional, then a coiled tail will result. Establishing baseline is important. I would also do the HOS on a specimen prior to onset of female stimulation for oocyte retrieval.

2) Does anyone feel any optimism that testis biopsy might yield motile sperm, which could then be used in an ICSI procedure?

If the results from HOS indicate viable sperm, then my optimism for motile sperm in a biopsy would be increased. To establish if the patient's seminal plasma might contribute to sperm stasis, I would have him collect in media and also expose washed control sperm with the patient's seminal plasma.

Good luck!

Christopher De Jonge, PhD, HCLD

Dr Charles Muller provided additional useful insights:

Regarding Andy Meacham's question of how to proceed with a case exhibiting 100% nonmotile sperm, I would like to suggest some lines of investigation in addition to the proposed use of HOS to choose sperm for ICSI.

First, a viability test is essential. Alternatives to HOS are eosin Y or trypan blue staining or use of a fluorescent DNA-binding probe such as Hoechst 33258.

If all the sperm in semen are "dead," we would not suggest ICSI using them. In our practice (Dr Richard Berger), we determine whether there is an immediate possible cause of cell death such as high reactive oxygen species generation by leukocytes, which might be addressed. If not, a vas or testicular aspiration is considered. We have seen

normal (for the site) motility from either vas or testis when semen sperm motility is poor.

Second, if some of the sperm are apparently live, we would attempt to stimulate motility using pentoxifylline. Surprisingly, this has worked in some cases of 0% motility. The induced motility may or may not be of sufficient quality and quantity to consider intrauterine insemination (IUI) or in vitro fertilization (IVF). But, even if there is only twitching motility, this may be sufficient to choose sperm for ICSI. The pentoxifylline is washed out of the sperm preparation before any of the insemination procedures. This also avoids having to use HOS to choose nonmotile sperm.

Third, if no sperm respond to pentoxifylline, medical, genetic, or electron microscopic evidence could be gathered to rule out an immotile cilia syndrome, followed by genetic counseling.

Good luck with this case!

Charles H. Muller, PhD, HCLD

Dr Marc Goldstein advocated a strictly surgical approach (as a surgeon, I have to admit a certain fondness for his point of view):

Do a testicular retrieval fresh at the time of IVF/ICSI. You will probably find motile (twitching) sperm. This is much more reliable than trying to identify viable sperm in a 0% motile ejaculate.

Sincerely, Marc Goldstein, MD, FACS

On the other hand, Dr Dawn Kelk argued the virtues of a laboratory-based strategy (Regarding Dr Meacham's question about 100% nonmotile sperm):

I have seen a couple of cases like this with 2 different causes. Do you know if this gentleman has Kartagener syndrome (I've also heard it called immotile cilia syndrome)?

I would do an HOS test and an eosin-nigrosin stain. Both tests are quite simple. You can perform ICSI using the HOS test. It is technically difficult to pick up curled sperm that have been exposed to HOS solution. But you can pick up the sperm from culture media, transfer your needle into a drop of HOS solution, hold the sperm near the opening of the needle, and allow the HOS solution to diffuse into the needle, and you can watch the sperm start to curl inside the ICSI needle. As soon as you see the sperm tail curl, you can move to a polyvinylpyrrolidone drop, break the tail, and perform the ICSI. This particular couple had twins using this technique.

In the other case, the individual simply didn't follow proper collection technique and had been using Lubriderm lotion. As soon as he collected without the Lubriderm, his motility was in the normal range.

If you can be sure that you have live/viable sperm, I don't know of any reason to perform a biopsy, but I'd be interested in others' thoughts.

Dawn A. Kelk, PhD

Finally, Dr Arnold Belker weighed in with the voice of experience in the following response:

I agree with Marc Goldstein's response. Indeed, I reported (*J Urol.* 1998;160:2058–2062), along with Dick Sherins and other members of his group, that testicular sperm obtained by testicular epidymal sperm aspiration from men with necrostermia would be useful for IVF/ICSI. The motility of testicular sperm from such men ranged from 0% to 10%, but the median viability using eosin Y dye exclusion ranged from 55% to 75%.

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