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Phosphodiesterase type 5 (PDE5) inhibitors: looking beyond erectile dysfunction

A round-table meeting to discuss the management of erectile dysfunction was held in London in June. Participants heard about the cardiac safety and cardiac potential of PDE5 inhibitors, and agreed a number of points about the clinical benefits and use of these agents. This supplement contains a report of the meeting.

Participants at the meeting

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Introduction

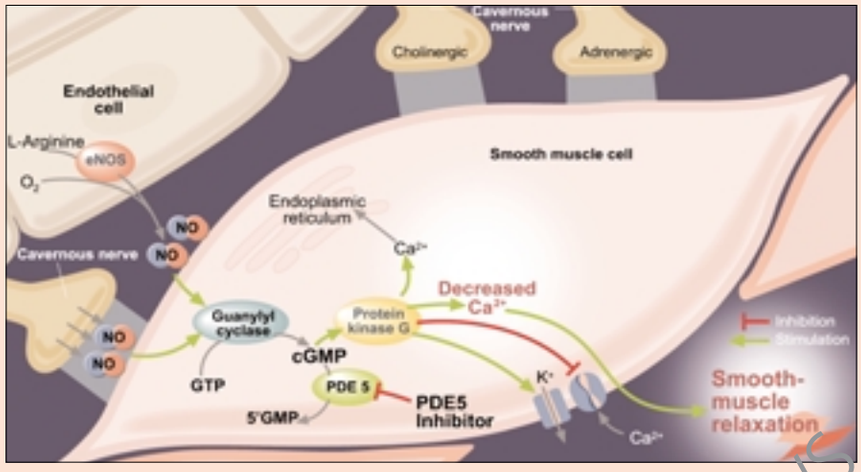
Erectile dysfunction (ED) is common. Though men are reticent about seeking help, some degree of ED is believed to affect up to 52% of men between 40 and 70 years of age. Patients with hypertension, diabetes, a history of smoking and hyperlipidaemia have an increased incidence of ED: about 70% of cases of ED have a vascular origin, and of these roughly half have diabetes.

ED may be a marker for other diseases: patients who present with ED should be assessed for previously undiagnosed conditions such as diabetes, ischaemic heart disease, hypertension and benign prostatic hyperplasia. Nonetheless, 80% of patients with ED are at low cardiovascular risk.

PDE5 inhibitors in erectile dysfunction

Phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil and vardenafil inhibit the

Figure 1. Mechanism of action of PDE5 inhibitors



Adapted from Lue T. *N Engl J Med* 2000;**342**:1802-13. ©2001 PW

breakdown of cyclic GMP (figure 1) and improve the rigidity and duration of erections. Early studies with sildenafil showed that it had a good safety profile, with an ED success rate of up to 80%, when used according to manufacturers' instructions. For example, the first phase of prescription event monitoring of cardiovascular events in 5,600 sildenafil users in primary care concluded that there was no evidence of a higher incidence of fatal myocardial infarction (MI), ischaemic heart disease or stroke among men taking sildenafil. Further studies have shown that there is no evidence of adverse events in stable male patients with severe coronary heart disease providing that they are properly advised and that sildenafil does not change the onset, extent or severity of ischaemia in men with known coronary artery disease.

In patients with cardiovascular disease, ED treatments are used in the same way as for other patients, except that for patients taking nitrate therapy or nitric oxide donors such as nicorandil all PDE5 inhibitors are contra-indicated.

What was of interest from the MI and mortality studies was that the MI and mortality rates were actually lower in the presence of PDE5 inhibitors than in the placebo group. In fact, PDE5 inhibitors may be beneficial to the cardiovascular system, with a potential future role in the treatment of hypertension and cardiac failure.

The major difference between tadalafil (Cialis) and sildenafil (Viagra) is duration of action. Sildenafil is effective in about 30 minutes, with a peak plasma concentration at one hour and then a sustained effect for 4–6 hours. Vardenafil is very similar in terms of duration of onset, action and efficacy. By contrast, the plasma concentration of tadalafil peaks at about two hours. The half life of tadalafil is 17 hours and its duration of action may extend to over 36 hours.

All three drugs have a similar ED efficacy, but tadalafil's longer duration of action may mean that the couple can be more spontaneous about their sexual activity. However, this longer duration of action could be a disadvantage in some cardiovascular patients who may need to use a nitrate within that time window.

There is less visual disturbance with tadalafil because it has a minimal effect on PDE6. Tadalafil does have a greater effect on PDE11, which is found in myocytes, but there is no evidence of any inotropic action and no evidence that it prolongs the QT interval.

Safety of tadalafil

The cardiovascular safety of tadalafil has been examined in phase II and phase III clinical trials. Cardiovascular adverse events in 26 double-blind clinical studies, involving a total of 3,666 tadalafil-treated patients and 1,437 patients taking placebo, are illustrated in table 1. It can be seen that the composite end point of MI/ischaemia/possible ischaemic symptoms occurs less often with tadalafil (0.63%) than with placebo (1.04%): in other words, it is non-inferior. Data for other entities such as congestive heart failure, arrhythmias and cerebrovascular events are very similar to those seen with placebo.

The incidence of MI in all clinical studies of tadalafil shows that, just as with sildenafil, the figure is slightly lower than with placebo.

Safety of vardenafil

The cardiovascular safety of vardenafil is also reassuring and has been reviewed by Kloner in an analysis of five placebo-controlled trials. The incidence rates of selected cardiovascular adverse events in this review were similar to placebo. Exercise-induced ischaemia has been shown not to be adversely affected by vardenafil during an exercise stress test in men with known coronary artery disease.

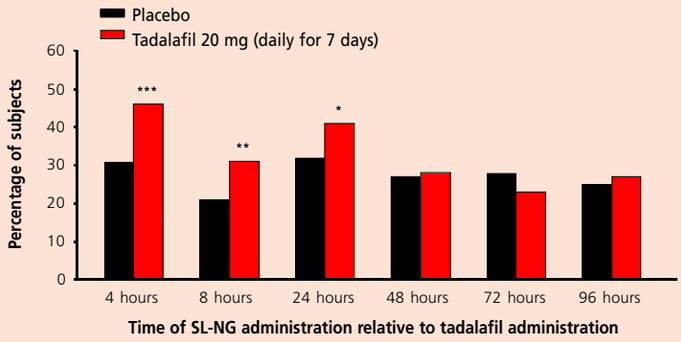
Alpha blockers in combination with sildenafil and tadalafil

Alpha blockers are used for the treat-

Table 1. Cardiovascular adverse events in 26 double-blind clinical studies using tadalafil

Event	Placebo (N=1,437) (%)	Tadalafil (N=3,666) (%)
Myocardial infarction/ischaemia/ possible ischaemic symptoms	1.04	0.63
Congestive heart failure	0.07	0
Ventricular arrhythmias	0.7	0
Cerebrovascular events	0	0.05
Syncope/hypotension/possible hypotensive symptoms	0.42	0.14
Supraventricular arrhythmias	0.07	0
Other arrhythmias	0	0
Other cardiovascular events	0	0
Conduction defects	0.07	0.08
Subjective rhythm/rate	0.42	0.74

Figure 2. Percentage of subjects with standing SBP < 85 mmHg in a study comparing the effects of tadalafil and placebo plus sublingual nitroglycerin



* P<0.05 *vs.* placebo; ** P<0.01 *vs.* placebo; *** P<0.001 *vs.* placebo

ment of benign prostatic hypertrophy (BPH) as well as hypertension. A study performed by Pfizer found that there was a chance of drug interaction, causing postural hypotension, between sildenafil and doxazosin. It is advised that doxazosin and sildenafil should be separated by at least four hours, and that the patient should be careful on standing when the doxazosin is taken.

This potential drug interaction could be of greater concern with a longer-acting PDE5 inhibitor such as tadalafil. Lilly performed a study to examine the effect on blood pressure of tadalafil 20 mg (the maximum available dose) compared to placebo in patients being treated with doxazosin 8 mg. The study found that the mean maximal post-baseline falls in standing systolic blood pressure (SBP) and standing and supine diastolic blood pressure (DBP) were significantly greater during tadalafil treatment, with a difference from placebo of -4/-3 mmHg supine and -10/-5mmHg standing. There were 18 patients in each group: five patients in the doxazosin plus tadalafil group had a standing SBP < 85 mmHg, and five had a > 30 mmHg drop in standing SBP from baseline (compared with one and two patients, respectively, in the doxazosin plus placebo group).

Though the difference between the two groups was not significant, because of the hypotensive outliers, clinical policy is determined by the outliers for safety reasons. Thus the current recommendation is that if doxazosin and tadalafil are to be co-prescribed, then the tadalafil is to be taken in the morning and the doxazosin to be taken in the evening while the patient is lying in bed (because there is no effect on supine SBP). This temporal separation is an important cardiovascular guideline for the use of the PDE5 inhibitors and alpha blockers.

There are alternative alpha blockers, such as tamsulosin, which selectively affect the prostate and do not have any haemodynamic effects. Comparing the effects on blood pressure of tadalafil 10 mg and 20 mg against placebo in patients being treated with tamsulosin 0.4 mg, no patients had a standing or supine SBP below 85 mmHg or DBP below 45 mmHg. The numbers of patients in each group with a reduction of more than 30 mmHg in standing SBP were similar (one of 18 patients in the tamsulosin plus placebo group, and two of 18 patients in both the tamsulosin and tadalafil treatment groups).

The conclusions were that, in these healthy subjects, co-administration of tamsulosin and tadalafil gave reductions in blood pressure that were neither dose-related nor clinically meaningful; and therefore in patients with ED and BPH, a selective alpha blocker might avoid potentially disadvantageous significant drops in blood pressure.

Questions and answers

Q: Isn't doxazosin used more in America than in the UK? Not many urologists in this country prescribe doxazosin rather than a selective agent, do they?

A: In diabetes clinics it is used as an add-on antihypertensive, and may often be used in men with erectile dysfunction.

Q: Moxonidine, another centrally acting agent, may also be favoured for blood pressure treatment in diabetic men with ED. Epidemiological data show that getting the SBP below 130–140 mmHg is associated with reduced cardiovascular risk. Is there a similar interaction between moxonidine and PDE5 inhibitors?

A: Studies need to be performed, certainly, to find that out.

Q: It is highly unsatisfactory to say to the patient that he has to take his drugs at a particular time of day. If there is a strong indication for a PDE5 inhibitor, would it not be better to prescribe other drugs that do not have this potential for interaction?

A: As regards treatment of BPH, we should be using tamsulosin or another selective agent. As regards hypertension, if we use doxazosin then we have to heed these cautions about timing and position and we should perhaps use an alternative antihypertensive agent such as an angiotensin receptor blocker, which also causes less ED and which in practice is one of the first-line treatments for hypertension in diabetes anyway.

Case report 1

A 56-year-old man with ED was referred following successful percutaneous coronary intervention (PCI). His ED had developed before his angina, for which he had been treated with atenolol and isosorbide mononitrate (ISMN) before his PCI. He was now well, with no limitation of exercise, but was still taking ISMN and atenolol. As ISMN is a contra-indication to a PDE5 inhibitor and of no prognostic value, it was discontinued. One week later he was reviewed.

He was still asymptomatic. He underwent a treadmill exercise test as a precaution, and managed nine minutes of the Bruce protocol without symptoms or ECG evidence of ischaemia.

His ED was successfully treated with tadalafil 20 mg. He was instructed to avoid the use of sublingual GTN for the 48 hours after taking tadalafil.

- ED may be a marker of silent vascular disease
- Nitrates can be discontinued safely in many patients, allowing ED treatment with a PDE5 inhibitor

Table 2. Management of ED according to cardiovascular risk at presentation

Low risk	Intermediate risk	High risk
Controlled hypertension Asymptomatic, with fewer than 3 risk factors for CAD (excluding age and gender) Mild valvular disease Minimal/mild stable angina Post successful revascularisation CHF NYHA class I	MI or CVA within previous 2–6 weeks LVD,CHF NYHA class II Murmur of unknown cause Moderate stable angina Heart transplant Recurrent TIAs Asymptomatic but > 3 risk factors for CAD (excluding age and gender)	Severe, unstable or refractory angina Uncontrolled hypertension (SBP > 180 mmHg) CHF NYHA class III or IV MI or CVA within last 14 days High-risk arrhythmias Hypertrophic cardiomyopathy Moderate/severe valve disease

Key: CAD = coronary artery disease; CHF = cardiac failure; NYHA = New York Heart Association; MI = myocardial infarct; CVA = cerebrovascular accident; TIA = transient ischaemic attack

Adapted from: Kirby M. Erectile dysfunction and vascular disease. Blackwell Publishing, 2003

Nitrates and PDE5 inhibitors

The big issue that will worry many clinicians in relation to nitrates and PDE5 inhibitors is the long duration of action of tadalafil.

One sildenafil study has shown that if healthy volunteers are given first 100 mg sildenafil (the maximum available dose) or placebo and then sublingual nitrates, the hypotensive effect of the combination is no longer present at six hours, implying that sublingual nitrates at that point would be safe.

A similar study has been performed using tadalafil 20 mg (the maximum available dose) and sublingual nitrates. Some 151 healthy subjects, including subjects with controlled diabetes and hypertension, completed this randomised, double-blind, placebo-controlled, two-period crossover study. The objective was to determine whether tadalafil augmented the hypotensive response to sublingual nitroglycerin 0.4 mg dosed 4,8,24,48,72 and 96 hours after seven daily doses of tadalafil. The primary end point was the number of subjects having a minimum standing SBP below 85 mmHg.

As predicted, a hypotensive effect was seen with tadalafil, and it took 48 hours for the percentage of subjects in the tadalafil and placebo groups with a standing SBP < 85 mmHg to equate (figure 2). Unfortunately, 36-hour data were not measured so the difference between the two groups at 36 hours is unknown.

The other drug to consider with respect to this question is nebivolol, which is claimed to have similar endothelial properties. We have to assume that it may be like nicorandil until we have data to show that it is safe (or that it is not). Atenolol can be used in the meanwhile. Safety data on nebivolol are expected in the near future.

Questions and answers

Q: What about patients who are on antihypertensives already? Probably 80–90% of patients in CHD clinics are taking a number of other drugs such as beta blockers and angiotensin converting enzyme inhibitors. Would adding a PDE5 inhibitor or a nitrate make any difference to their blood pressure?

A: There does not seem to be any interaction between the PDE5 inhibitors and drugs other than the nitrates or nicorandil; there is no hypotensive effect from the PDE5 inhibitor *per se* in multiple therapy. What we do not know is how effective the compensatory mechanisms might be in patients on multiple therapy, and whether there is so much dilatation in the vessels already that there is little potential for a further drop.

There is a great variation between patients in their response to nitrates – in some the blood pressure falls steeply and in others there is very little response – and this response is unpredictable. Doctors should be advising against sublingual nitrates for 48 hours after tadalafil because of the risk of a postural drop.

Q: How big a drop in blood pressure is this, and how clinically relevant is it? It may be of almost no relevance in clinical practice. Should we therefore currently be favouring short-acting or long-acting PDE5 inhibitors in men with overt IHD?

A: We know that about 80% of ED patients are in the low-risk category when their cardiovascular function is assessed (at the Guy's Hospital clinic), and so for them this potential drug interaction is probably largely irrelevant and any PDE5 inhibitor could be used. However, for the 20% of patients at intermediate or high risk, a shorter-acting agent might be preferable.

It is generally a good idea, if you come across a clinical situation that you are not sure about, to use a short-acting agent rather than a long-acting one.

Q: Are there ways to improve patients' recall and understanding of their drugs (and possible drug interactions)?

A: In the Guy's Hospital clinic 70% of cardiac patients are treated with PDE5 inhibitors, and 30% of them carry a short-acting nitrate. All our patients sign a consent to self-medicate form, saying that they under-

Case report 2

A 60-year-old man with diabetes has been happily married for 25 years. He was diagnosed with type 2 diabetes six years ago. He also has hypertension, for which he takes bendrofluazide 2.5 mg and atenolol 100 mg. His diabetes is being treated with metformin 0.5 g tds.

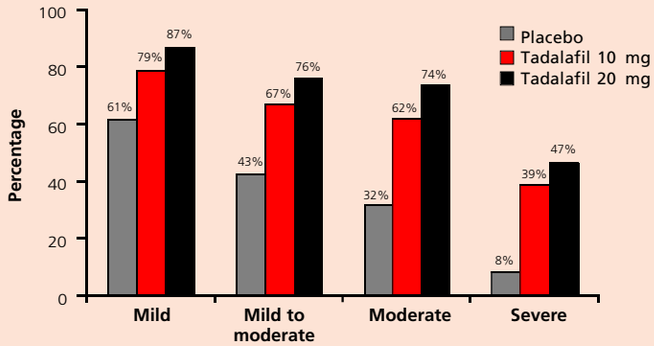
At his last two visits for routine checks he has appeared depressed and lacking in motivation to address his lifestyle issues. When the subject of sexual activity was mentioned, he acknowledged the fact that he had had been having problems with his erections, and for the last six months he had been finding great difficulty in achieving an erection at all. Nocturnal and morning erections are both absent.

He believed that his problems were due to his getting old, and was relieved to learn that his problem had a physical cause and that neither he nor his wife were to blame.

He was successfully treated with a PDE5 inhibitor, and subsequently both his mood and his diabetic control improved.

- Professionals need to raise the issue of sexual function in the at-risk population
- ED may cause both depression and lack of motivation
- Successful treatment enhances quality of life, improves relationships and may improve concordance with lifestyle advice

Figure 3. Percentage of successful intercourse attempts[§] by ED severity in subjects taking placebo or tadalafil



[§] Positive response to SEP Question 3: Did your erection last long enough to have successful intercourse? ED severity was classified using baseline IIEF EF domain scores as follows: Severe (1–10), Moderate (11–16), Mild to moderate (17–21), Mild (22–25), Normal (26–30)

stand that they must not overlap their treatments for 12 hours (or more, depending on the agent). We ask them to sign a form which describes what has been discussed. The patient keeps a copy and another copy is sent to the patient's GP.

We are reviewing the last two years' work to see whether patients are having any difficulties in combining therapies. So far there have been no reported problems, and of the 30% of patients who carry a nitrate spray, 90% say they carry the spray but never use it. It would be a shame if patients were to be denied PDE5 inhibitor treatment simply because they carried a nitrate spray.

In this specially constructed clinic we have been stopping patients' oral nitrates and nicorandil to facilitate PDE5 inhibitor introduction and have been successful in 27 men without adverse events.

It is absolutely crucial to use risk stratification in these patients. We have seen more than 300 patients in this clinic and by minimising the risk of treatment, we have had no untoward episodes.

A simple guide to risk stratification is given in table 2.

The lower-risk patients may receive any PDE5 inhibitor. In borderline cases we might start with sildenafil and monitor the patient's progress. For those at higher risk, we would not prescribe a PDE5 inhibitor without detailed cardiac assessment.

Q: Doesn't a consent form imply that there is a risk associated with treatment, and that patients are right to be worried about taking it?

A: Talking through a patient's condition and treatment represents an opportunity to educate the patient. Many of the patients referred to the Guy's Hospital clinic have difficult cardiac problems such as continuing angina post-bypass or quadruple antianginal therapy which is not fully effective so we have to be sure in that setting.

Q: Do you really advocate written consent for all treatments, and is it legally watertight?

A: It would be helpful in that a patient who signs a form such as this is taking some responsibility for managing his condition.

Consensus statement about nitrates and PDE5 inhibitors

- The vast majority of cardiac patients fall into the low-risk category, and therefore the interaction between nitrates and PDE5 inhibitors is unlikely to be an issue
- For those patients at intermediate or high risk, or when the clinician is concerned, a shorter-acting agent would be preferred
- Individual units might wish to introduce for patients (after suitable discussion of wording) an educational form to self-medicate, or to formalise the doctor-patient agreement in some other way. Accurate documentation of the information given to patients is useful

Exercise tolerance

A treadmill study looked at the effect of sildenafil on exercise time in patients with positive exercise tests and documented coronary disease. Sildenafil gave a slight but significant increase in exercise duration, exercise time to ST segment depression and total exercise time – it tested positively as an antianginal agent. It provided evidence that sildenafil, when superimposed on beta blockers or calcium antagonists, might facilitate sexual intercourse in stable angina patients at the same time as treating their ED.

A similar test done with tadalafil did not show a difference between tadalafil and placebo in time to an ischaemic end point. However, these patients' symptoms were very mild, they did not have ED, and eight of the 46 subjects were female. In another study published in the *Journal of the American College of Cardiology*, vardenafil had no impact on exercise time or ST segment depression.

It can be concluded that in a stable ischaemic population, PDE5 inhibitors do not have any disadvantageous effects on exercise performance – that is, they are non-inferior to placebo – and, because of their mode of action, there is a potential advantage.

Other cardiac studies have been performed, including QT interval studies and cardiac contractility studies. The results with tadalafil are identical to those with sildenafil, and no adverse effects have been found. No evidence of coronary steal was found in acute exercise testing studies.

In summary:

- The incidence of cardiovascular adverse effects in 26 double-blind studies was low and was not different from that observed in placebo-treated patients
- The incidence of MI in tadalafil clinical trials was low, and was no higher that that observed in placebo-treated patients or the age-standardised male population
- There is no evidence of an effect of tadalafil on ventricular repolarisation, cardiac contractility, myocardial blood flow or time to ischaemia
- Tadalafil 20 mg augmented the blood pressure-lowering effect of the alpha blocker doxazosin 8 mg
- There was no clinically significant augmentation of the blood pressure-lowering effect of the selective alpha blocker tamsulosin

- Blood pressure interaction with nitrates is no longer detected when nitroglycerin is administered 48 hours after tadalafil

Question and answer

Q: What is the position with long-acting nitrates?

A: The recommendation is five half-lives. With short-acting nitrates a definite dip in blood pressure is seen but with the longer-acting nitrates this is much less marked. In certain situations nitrate tolerance may develop and the nitrate may not really act as a nitrate.

Benefits of PDE5 inhibition

The more severe the erectile dysfunction, the greater the relative benefit from tadalafil. You would expect that the more ED the patient had, the less likely it would be for the drug to be effective, but this is not the case. Figure 3 shows the percentage of successful intercourse attempts by ED severity in subjects taking placebo or tadalafil 10 mg or 20 mg. In mild ED patients taking placebo do well because they benefit from discussing their symptoms with the doctor. As the ED becomes more severe, the difference between placebo-treated and tadalafil-treated groups becomes greater. Twice as many patients with moderate ED had successful intercourse attempts on tadalafil treatment versus placebo, and with severe ED 47% of tadalafil-treated patients had successful intercourse attempts as against only 8% in the placebo group. The scale of difference between these treatment groups suggests that PDE5 inhibitors might have some additional property that works to patients' cardiovascular advantage.

When arterial vasoconstriction and angiotensin II activation occur, the angiotensin II stimulates PDE5. If an angiotensin II antagonist were used in such circumstances, it could improve both vasodilatation and erectile dysfunction. It is possible too that PDE5 inhibitors could be potentiated.

Angiotensin II antagonists facilitate erectile function as well as causing muscular relaxation. This was observed in a very good paper comparing valsartan with carvedilol. Could there be a two-way process such that PDE5 inhibition potentiated the effects of angiotensin II antagonism?

If this happened, then cyclic GMP levels would rise, as would urinary excretion of its breakdown products (which is seen in pulmonary hypertension), and PDE5 inhibition might have potentiated benefits throughout the vasculature.

Potential clinical areas of interest are hypertension, pulmonary hypertension, Raynaud's phenomenon and cardiac failure: all have this common denominator of arteriolar vasoconstriction.

Case report 3

A 65-year-old man presented with a two-year history of erectile dysfunction (ED). He had an extensive cardiac history. An angiogram in January 2001 showed severe coronary disease and he had a stent angioplasty. Afterwards he developed in-stent restenosis and required a second angioplasty.

He had noticed a decrease in the quality of his erections about the time of his cardiac diagnosis, and by the time he presented in clinic he had complete ED. His wife was not able to attend the clinic but was aware of the appointment and supportive of his seeking treatment. He said that the ED had not caused any relationship difficulties. Current medication included atenolol, simvastatin, nicorandil and aspirin.

The patient commented that he was now very active, and that he did not feel limited by angina symptoms. Nicorandil was discontinued and the patient was given a sublingual GTN spray in case of angina. Two weeks later he was still asymptomatic and he performed an excellent exercise test with no symptoms or ischaemic changes.

The treatment options were discussed. He said that he would prefer an oral agent for his ED, and chose tadalafil because he thought that its longer duration of action would allow more spontaneity. Tadalafil 20 mg was prescribed. He was counselled on the importance of not overlapping his GTN spray for a 48-hour period pre- and post-tadalafil, and on what to do in the event of chest pain. (This standard time period is specified to avoid patient confusion.) A consent to self-medicate form was used.

At follow-up eight weeks later he reported an excellent result – his sex life was back to normal.

- Consider taking patients off their long-acting nitrates if they are asymptomatic
- Ensure patients are properly counselled about how to take their ED drugs
- Ensure that the needs of partners are taken into consideration, even if they are not present

Hypertension

If tadalafil is added to a calcium channel blocker such as amlodipine, there is no change in systolic or diastolic blood pressure because amlodipine has already caused vasodilatation. However, if tadalafil is added to a drug that is not a vasodilator, such as the beta blocker metoprolol (figure 4), then both systolic and diastolic blood pressure fall in comparison to placebo.

In a normotensive patient given a PDE5 inhibitor, a blood pressure drop of up to 10/7 mmHg is observed, which is not clinically irrelevant. If you were to give one of these drugs to a hypertensive patient, would there be a greater fall in blood pressure because the system is in some way upregulated? There is only one study, which used sildenafil 50 mg in eight hypertensive patients. With placebo, the drop in blood pressure was 6 mmHg systolic and 3 mmHg diastolic. By comparison, with sildenafil there was a 24 mmHg drop in systolic pressure and an 8 mmHg drop in diastolic pressure. The one-hour SBP was also significantly lower in sildenafil-treated patients (135 *vs.* 144 mmHg).

Does tadalafil have a potential use as an antihypertensive agent, particularly since it can be given once daily? Perhaps the nitrate-PDE5 inhibitor interaction need not always be counterproductive, but could be used to advantage in patients with resistant hypertension.

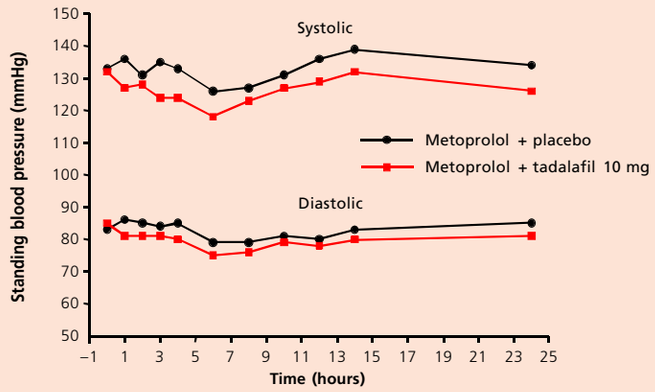
PDE5 inhibitors could be important cardiovascular drugs with significant therapeutic potential. Clinical trials have shown that it can be very difficult to bring blood pressures down to target, but PDE5 inhibitors have a different mechanism of action and could bring the blood pressure down further. In addition, there is a high incidence of ED in patients with hypertension – 17% before treatment – so PDE5 inhibitor treatment could treat both the hypertension and the erectile dysfunction.

Question and answer

Q: Is there any evidence of tolerance?

A: There is no evidence of tolerance with PDE5 inhibitors with respect to chronic dosing for ED and blood pressure lowering but that has only been studied in normotensives. It has been studied in hypertensives with sildenafil, but with intermittent dosing, which is quite different.

Figure 4. Effects on blood pressure of metoprolol with either placebo or tadalafil, showing a drug interaction



Data on file, Lilly ICOS LLC

Pulmonary hypertension

Sildenafil has transformed the lives of adults and children with pulmonary hypertension. There are adults who have been taking sildenafil four times a day for two and a half years with no deterioration in their exercise performance, and formal studies are being performed in children as well. Pfizer is hoping for a licence in 2004/5 for use of sildenafil four times daily in pulmonary hypertension. If all PDE5 inhibitors work in the same way, then tadalafil once daily could be the logical next step.

There are other studies examining the effect of sildenafil in pulmonary hypertension secondary to connective tissue disorders. Studies are needed in HIV-positive patients with pulmonary hypertension, who have a life expectancy of only six months. A drug that could improve their pulmonary function could lengthen their lives quite significantly. Clearly, such studies would need to take into account other drugs that the patients would be taking but results could be obtained in an unusually short-time period.

Cardiac failure

There are ongoing studies of PDE5 inhibition in cardiac failure. One study presented at the American Heart Association meeting last year reported results in seven male patients with NYHA class III heart failure and an LVEF of 20+/-5%. Sildenafil was given after right heart catheterisation: it increased maximal oxygen consumption, reduced both baseline and exercise pulmonary vascular resistance, and gave haemodynamic improvements including increased cardiac output and stroke volume. There were no significant changes in mean arterial pressure.

Raynaud's phenomenon

There are anecdotes about improvements in Raynaud's phenomenon in patients who take PDE5 inhibitors.

A study reported in the rheumatology literature described how 50 mg sildenafil given daily for three years cleared up Raynaud's-associated ulcers and symptoms in 10 patients. When the drug was stopped all patients became worse, and when the drug was recommenced they all improved again. Such anecdotes are worth investigating, and again a longer-acting agent might be advantageous.

Endothelial dysfunction

The common denominator in all these conditions is probably endothelial dysfunction. Brachial artery diameter increases acutely and chronically after sildenafil administration in diabetic and non-diabetic subjects, and sildenafil improves the augmentation index. The acetylcholine constriction response in the presence of diseased coronary arteries is improved by sildenafil. The normal dilatation response in normal vessels is not affected. Thus there is clearcut evidence of improved endothelial function with PDE5 inhibitor treatment.

Cardiovascular summary

To summarise matters from the cardiac perspective, PDE5 inhibitors have a good safety record in cardiac patients who are properly assessed, nitrates and nitric oxide donors should be avoided with these agents, and caution is needed with doxazosin co-administration.

Future avenues

The effects of PDE5 inhibitors on endothelial function could be central to their future usage. If they had a role in the prevention of vascular disease in diabetes, that could be extremely

Key points in management of erectile dysfunction

- For the vast majority of patients, the PDE5 inhibitors have a good safety profile
- Caution applies in relation to nitrates, nicorandil, nebivolol and doxazosin
- There is no evidence base that these agents are cardiologically disadvantageous
- It is up to the physician or nurse to enquire about erectile dysfunction in patients with cardiovascular risk factors such as hypertension and diabetes
- Risk stratification is crucial in safe management of these patients
- If the doctor or nurse is uncomfortable with treating erectile dysfunction then the patient should be referred
- Female sexual dysfunction is important. As yet no clearcut beneficial effect of PDE5 inhibitors has been demonstrated in female sexual dysfunction

Useful websites

- American Diabetic Association: www.diabetes.org
- American Heart Association: www.americanheart.org
- British Association for Sexual and Relationship Therapy: www.basrt.org.uk
- British Cardiac Society: www.bcs.com
- British Heart Foundation: www.bhf.org.uk
- Diabetes UK: www.diabetes.co.uk
- Heart UK: www.heartuk.org.uk
- The Impotence Association: www.impotence.org.uk
- Société Internationale d'Urologie: www.siu-urology.org
- www.heartsforlife.com

important. They might have a role in the treatment of endothelial dysfunction and in smooth muscle relaxation. We do not yet know about their role in improving prognosis but there is no evidence from the data that we have that there would be an adverse effect from using these agents in heart failure and pulmonary hypertension, which carry a very poor prognosis at present.

Questions and answers

Q: Can you comment further on the potential for these drugs?

A: Their mode of action makes them different from the calcium antagonists, even though they act like them. Though they open potassium channels like nicorandil, they obviously have other effects within the cell. They improve endothelial function: the scale of improvement in endothelial function seen with these agents is similar to that seen with the statins.

Q: If you have someone who is maximally treated with a statin, do you have the same effect on endothelial function on adding a PDE5 inhibitor?

A: That is a very good question. It would be a really important study, and it would not be that difficult to do. Metabolic syndrome and syndrome X have some underlying endothelial dysfunction, too, and are difficult conditions to manage at present.

Q: What is the link between statins and erectile dysfunction?

A: It is a mixed story. With the lipid-soluble statins such as simvastatin and atorvastatin, erectile dysfunction can certainly be observed within 2–3 weeks: there is less ED with pravastatin. This may be a central action or a drug interaction but is probably not a function of how far the cholesterol is lowered.

The statin effects may be related to coenzyme Q10 because that has a role in smooth muscle as well as skeletal muscle function. Atorvastatin and simvastatin have more of an effect on coenzyme Q10 than pravastatin.

Q: It would be difficult to do a heart failure study using PDE5 inhibitors because, in contrast to HIV-positive pulmonary hypertension patients, there would be fewer end points. It becomes even more difficult since the study would have to be an add-on study.

A: A heart failure study would be looking at symptomatic improvement, using exercise capacity perhaps, rather than at prognosis. If PDE5 inhibitors turned out to have a large influence on quality of life, then a prognostic study would need to include thousands of patients.

Q: There are areas of considerable importance regarding use of PDE5 inhibitors in diabetes aren't there? For example, it would be interesting to know whether you see the same blood pressure drops in type 2 diabetes with these drugs since the blood vessels of diabetic patients are nitric oxide-resistant.

Also, the aetiology of erectile dysfunction is slightly different and more complex in diabetics. A lot of data show that diabetic men have lower testosterone levels than age-matched non-diabetic men. Should we optimise these men's testosterone levels before using this class of drug, and would their response to PDE5 inhibitors be better if we did that?

A: The testosterone issue does not seem particularly important in the cardiac clinic, but it would be very interesting to compare these data with data from a diabetic clinic.

Further reading

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