A Peripatetic Discourse on Sildenafil

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"Whoso foresaketh all desires and goeth onwards free from yearnings, selfless and without egoism- he goeth to Peace." (The Bhagavad Gita ; second discourse #71)

Far from being a muni or a yogi, many years have passed since I have lost all the desire to write medical articles for medical journals. Along with this several other desires have also died in me. The following is a peripatetic discourse, not a formal paper, on sildenafil, in response to a request repeated several times by a close Friend of Old Times, Dr M.A.Youssefnia, now a prominent cardiac surgeon at several hospitals, president of the Cardiac Surgeon's Society, and many other professional organizations.

The imitation of the occidental methods, including "publish or perish" motto, has driven the underdeveloped world to the brink of insanity and chaos, with a mushrooming of many sham journals, seminars, conventions, workshops etc, etc most of which are ruminations of works already published, or mock imitation of original research works, with a premeditated, selective "publish or perish "effect at local levels.

Now having vanished from the field, I am immune to perishing. Therefore the response of the author to his close friend's request is neither a paper, nor a research report. It is simply a soliloquy.

"If nobody listens to the word of your heart, walk alone, walk alone, walk alone." (Rabindranath Tagore)

1-Years ago, in the 1980s, I realized that we desperately needed NO for pediatric patients after cardiac surgery. Pulmonary hypertension reactive or fixed, played havoc in the ICU.

So I started to pass the bureaucratic maze for buying NO for the pediatric cardiac ICU. Eventually all hurdles behind me, I requested buying NO cylinders. Needless to say that NO used for medical purposes must be pure, free from contaminants, not available locally. Eventually a company in Canada responded that NO cylinders could be shipped to the hospital, the price 20000$ each!

Well this was the beginning of the story, not "the beginning of the end"! So I never ordered NO cylinders, but I started searching for an alternative.

2-In the Golden Years of the Pfizer Company, New York, New York Viagra was marketed for the treatment of male erectile dysfunction. Having read the literature I learned that NO is constantly released by vascular endothelium, and almost immediately neutralized by phosphdiesterase 5.So the medication actually caused accumulation of endogenous NO in the body. Immediately I thought that we could use sildenafil in the postoperative pediatric cardiac patients, instead of inhaled NO. The drug being fairly safe and non-toxic proved ideal for the test. So I started to use sildenafil in children with pulmonary hypertension, and especially those whose pulmonary arterial pressure had to be kept low after cardiac operation. The drug worked marvel, and encouraged by the clinical response I used it routinely on my patients. A couple of my colleagues joined the wagon, whereas some others still after so many years, look at this work with disbelief, despite approval of sildenafil by FDA, for treatment of pulmonary hypertension a few years ago. Viagra is now marketed under the name of Revatio by Pfizer for treatment of pulmonary hypertension.

3- I would like to recapitulate the clinical uses of sildenafil. After each statement

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references are quoted.

I-Sildenafil was originally developed to treat male erectile dysfunction. The pathway of enzyme interactions for erection is complex. Interested readers could refer to JACC 2003; 43:185-186 and JACC 2003; 43:179-184.

II -Sildenafil is potentially useful in treatment of heart failure. It prevents peripheral effects of sympathetic stimulation in heart failure; it dilates the pulmonary and systemic vessels, thus reducing PVR and SVR, and it improves left ventricular diastolic function.

(Ref. Circulation 2005:112; 2589-2591 Circulation 2005:112; 2642)

III-Sildenafil ***has carddioprotective*** effect against coronary artery disease.

(Circulation 2006; 113:1708-1714)

IV-Sildenafil confers protection against ***ischemia in the heart, and has ischemic pre-conditioning effect.***

(Circulation 2005; 112:721-723
Circulation 2005; 112:2589-2591
Circulation 2006; 113:1708-1714)

V-Sildenafil has beneficial effects in treating drug-induced cardiomyopathies.

(Circulation 2005;114:1601-1610)

VI-Sildenafil is the only effective therapeutic agent for treating Raynaud's disease, and Raynaud's phenomenon. The author's experience with this drug in a 22-year-old girl with Raynaud's disease has been most gratifying.

(Circulation 2005; 112; 2980-2985)

VI-Releasing No by Sildenafil from endothelium is theoretically beneficial for patients with ***hypertrophic cardiomyopathy*** who have diastolic ventricular dysfunction.

We know one of the major endothelial factors released by the endothelial cells is NO.

We know that endothelium of vessels under the effect of shear stress (Tau) releases NO and prostacyclins. The substances released cause vasorelaxation, by reducing vascular tone. They prevent thrombosis and adhesion of mononuclear cells to the endothelium and they are antiproliferative. (Circulation 2008; 117:2044-2046). Therefore NO, one of the major products of endothelium has all the properties of preventing atherosclerosis and pulmonary vascular obstructive disease (PVOD). Sildenafil should have beneficial effects on ventricular diastolic dysfunction,because of releasing endogenous NO. Thus sildenafil is potentially a lusitropic agent.

(Circulation 2005:112; 2589-2591
Circulation 2005:112; 2642)

VIII-Many references have shown beneficial effect of sildenafil in reducing ***pulmonary hypertension*** (PH). The author's experience with sildenafil has shown the following results over several years:

1-Sildenafil is most effective in treatment of ***hyperkinetic pulmonary hypertension.*** The effect is dramatic.

We use sildenafil routinely in the cases of VSD, PDA with PH. Once you don't find a good gradient in a baby with VSD, and /or PDA, sildenafil is given orally and physical examination (PE) and echo examinations are repeated in 15-30 minutes after. If the pulmonary vascular bed is reactive the murmur of VSD or PDA appears and on echo a left to right shunt with increased gradient is observed.

The response is so rapid that I use sildenafil in the clinic for decision making. Initially Dr Soroush Ghafourian used sildenafil and tested the patient after a few days. Later I found out that the effect could be noted within 15-30 minutes after sildenafil administration. I have called this ***Soroush test.*** It is noteworthy that if an infant does not respond favorably immediately to Sildenafil, ***pulmonary vascular obstructive disease (PVOD)*** should be suspected.

There are now many references for the effect of sildenafil on pulmonary hypertension one is Circulation2007:115:2331-2339

1-Once pulmonary vascular obstructive disease (PVOD) sets in, ie tissue hyperplasia and plexiform changes have developed, the response to sildenafil is not so dramatic. In these cases the patient may not respond to therapy even after several years of therapy. However most patients do respond to some extent by a reduction of pulmonary artery pressure (PAP),as evidenced by improved symptoms.

2-I catheterize the patients with PH who are candidates for sildenafil therapy. This complete baseline study is a must for further evaluation of treatment. If at any time physical examination (PE), EKG, Chest X-ray and echo show signs of reduced PAP, I recatheterize the patient for documentation of the degree of response to therapy. The procedure is repeated until the patient becomes a candidate for surgery.

3-The dosage of sildenafil is a matter of controversy. The dosages reported in the literature are mostly homeopathic. As the drug is non-toxic higher doses could be used. I titrate the dose with the patient's response. At ICU the highest dose which does not cause worrisome systemic

hypotension is used. Although the effect of drug persists for 24 hours, for treatment of PH I administer the drug q12hrs, or even more often if necessary. A rule of thumb is 5 mg/kg per 24 hours for infants, and 50 to 150 mg per day in 2 or 3 divided doses in older children and adults.
(Also read J Am Coll Cardiol 2008;51:1527-38)

4-The use in children and adult girls is easy, however the dose should be small in the beginning, and depending on the tolerance the dose is increased to maximum tolerable levels.

5-In adolescent boys the drug must be given with caution and explicit description of priapism should be given to the parents and the patient. Priapism is an emergency, to be reported immediately to the physician.

6-I usually give the higher dose to girls and boys in the morning .Somehow I tend to believe that erection and other side effects are less during waking hours. The lower dose is given at the time of going to bed (hs).This is especially desirable since nasal obstruction could be troublesome at night interfering with sleep.

7-I now use sildenafil in adult cardiac patients under EECP. The drug is given with all the nitrous compounds including NTG off. Primary indications for sildenafil under EECP therapy are:

Male and female patients with PH due to left ventricular dysfunction, and those with sleep apnea.

Male patients whose general condition becomes so good that they want to have sexual intercourse. All precautions are explained explicitly with these patients using sildenafil.

8-I have had problems with pharmacists who are mostly unaware of uses of Sildenafil in females and children. Some have been sarcastic and some have been arrogant in their ignorance. Some physicians are also unaware of the indications, dosage and method of administration.

9-One practical point is that the morning dose, must not be taken on the empty stomach. The empty stomach in the morning contains lots of acid and enzymes. First a glass of water must be drunk. Then one waits for 15 minutes, then the drug is taken. Many mothers give sildenafil to their children just before breakfast. This defeats the purpose. One must wait at least 30 minutes before eating food. The pill should be broken at least in two parts. This allows rapid absorption in the small intestine. The protective cover of the pill delays absorption. After taking the medication the effect is noted 30 minutes after, with maximum effect noted 1 hour later.

The method developed by our nurses at the pediatric cardiac ICU ,is dissolving the pill in a few milliliters of water, then drawing the required dose from the solution in a syringe for oral administration. I rarely use this method for outpatient therapy.