The use of prostaglandin E\(_1\) for diagnosis and treatment of erectile dysfunction

W. Stackl*, R. Hasun, and M. Marberger

Department of Urology, Rudolfstiftung, Juchgasse 25, A-1030 Vienna, Austria

Summary. Since 1982, many substances have been used for intracavernous injection to produce erections. Because the first-generation drugs (phenoxybenzamine, papaverine) were associated with severe side effects, including priapism and fibrosis of the penis, it was important that a safe and effective substance for intracavernous injection be found. In our series of 550 men with erectile dysfunction who received a test dose of 20 \(\mu\)g prostaglandin E\(_1\), 385 (70%) developed an erection lasting more than 30 min. Side effects were minimal: only one patient required treatment for priapism, and no fibrosis was found. A total of 275 patients entered an autoinjection protocol. All of these men were capable of engaging in intercourse and experienced no major side effects. In conclusion, prostaglandin E\(_1\) is effective, safe and preferable to all other drugs currently used for intracavernous injection.

The intracavernous injection of vasoactive agents in animal models and human volunteers has advanced the understanding of erectile physiology and the approach to the diagnosis and treatment of impotence. Various agents have been used, including papaverine, phenoxybenzamine, thymoxamine, prostaglandin E\(_1\), or a combination of papaverine and phentolamine [10]. Due to its lack of severe side effects, prostaglandin E\(_1\) seems to be superior to other drugs used for this purpose [15].

History of prostaglandin

In 1913, Battez and Poulet [2] determined that the extract of human prostate contained a substance that lowered the blood pressure. In 1930, Kurzrock and Lieb [11] found that compounds of human ejaculate, later proven to be prostaglandins, caused both a contractile and a relaxing effect on the uterus. In 1935, von Euler [6] discovered a lipoid factor in the seminal fluid that caused smooth muscle relaxation and a decrease in blood pressure. Because he thought that this factor was created in the prostate, he named it prostaglandin. The first prostaglandins were actually isolated in 1957 [3], and their chemical structure was elucidated in 1962 by Bergström et al. [4]. By 1985, prostaglandin E\(_1\) had been shown to cause relaxation of the smooth muscle in the corpus cavernosum [8]. To date, the only approved clinical indication for prostaglandin E\(_1\) has been in the treatment of infants with patent ductus arteriosus [5].

Patients and methods

Between 1986 and 1989, 550 patients with erectile dysfunction were investigated. The age of the patients ranged between 16 and 83 years. In all, 15% were heavy smokers (>20 cigarettes/day), 8% were diabetics and 10% had hypertension; 10% had more than one of these factors. In 35 patients the cause of impotence was pelvic surgery, and 28 subjects had severe neurological diseases.

After a meticulous history had been obtained, an intracavernous injection of prostaglandin E\(_1\) (PGE\(_1\)) was given as the first diagnostic step in determining the etiology of the erectile dysfunction. In addition, the appropriate dose of PGE\(_1\) necessary for safe autoinjection could be calculated.

Prostaglandin E\(_1\)-test. All but 24 selected patients with psychogenic impotence received a PGE\(_1\) test dose of 20 \(\mu\)g. The 24 patients with psychogenic impotence received an initial test dose of 5 \(\mu\)g, which was then increased to 10 and 20 \(\mu\)g, respectively, at weekly intervals.

PGE\(_1\) (Alprostadil, Minprog, Upjohn Crawley, UK) at 0.5 mg/ml was mixed with 24 ml normal saline to make 20 \(\mu\)g/ml solution. (Since this solution is stable for 110 days at 8°C, for 45 days at 20°C and for 26 days at 30°C, it should be stored in a refrigerator.) The appropriate test dose was injected into one cavernous body with a 26-gauge needle. After the injection, the penis was squeezed for about 5 s to enable the transfer of drug to the contralateral cavernous body. The PGE\(_1\) test was defined as being positive if full erection was achieved after injection and maintained for at least 30 min without sexual stimulation.

Auto-injection of prostaglandin E\(_1\). Of 385 patients with a positive test, 275 entered an auto-injection protocol. The patients were instructed in the anatomy of the penis, especially the relation between the corpus cavernosum, the corpus spongiosum of the urethra and the dorsal...
neurovascular bundle. The patient and/or his partner was then instructed in the auto-injection technique. The injected dose ranged between 5 and 60 μg, and 4% of the patients varied their dose; the dose was calculated according to the result of the PGE$_1$ test, e.g. if a patient developed a 2-h erection after a 20-μg dose and desired a 1-h erection, the recommended dose was 10 μg.

Results

PGE$_1$ test

A positive response to the PGE$_1$ test was noted in 385 of the 550 patients, with the onset of erection occurring after 5–15 min (mean, 7.5 min) and with a duration of 0.5–7 h (mean, 2.3 h). In all, 24 psychogenically impotent patients showed a linear response between doses of 5, 10 and 20 μg PGE$_1$ and the duration of their erections.

Side effects included prolonged erections, pain at the injection site and during erection, and penile hematomas. Because erections lasting > 5 h were observed in five patients with severe neurological diseases, we reduced the test dose for neurogenically impotent patients to 10 μg. Subsequently, patients with neurological diseases who received the 10-μg dose had erections lasting only 0.7–3.2 h. One patient who had suffered a stroke 1 year prior to the PGE$_1$ test developed a priapism that lasted 48 h after receiving a 10-μg injection. He was initially treated with a Winter shunt and finally required the insertion of a penile prosthesis. In all, 7% of the patients complained of pain from the injection, 11% during the erection, and 44% both from the injection and during the erection. Only 1% of the patients who complained of pain required medication. In one patient the erection was treated with an epinephrine injection 3.5 h after the injection of 20 μg PGE$_1$, due to severe pain. Hematomas at the injection site were observed in 3% of the patients and resolved without sequelae. There was no significant correlation between the different risk factors (e.g. smoking, diabetes, hypertension) and the test results.

PGE$_1$ auto-injection

The injected dose ranged from 5 to 60 μg. The only side effect noticed in the auto-injection group was a well-tolerated tension within the cavernous body. During the learning phase of the auto-injection technique, subcutaneous injection occurred but no adverse sequelae were noted. Some patients reported a burning sensation after improper injection; of course, no erection occurred. In these cases we suggested a second injection 30 min later. In most patients the erection persisted after ejaculation. In the auto-injection group, no priapism or fibrosis was noted, even after > 400 penile injections in some individuals.

Discussion

Prostaglandin E$_1$ is a natural constituent of many mammalian tissues. In humans it is found in high concentrations in the seminal vesical and seminal plasma [18]. Roy et al. [13] have reported that human cavernous tissue can generate prostaglandins and thromboxans in vitro. The primary organs for the metabolism and inactivation of PGE$_1$ are the lung, liver and kidney. In a single passage through the lung, about 70% of the PGE$_1$ is metabolised [7]; its lack of systemic side effects can thus be accounted for by its rapid metabolism. Even in our patients with penile venous leakage, in whom one would predict the highest serum PGE$_1$ levels following intracavernous injection, no changes in blood pressure or other adverse systemic reactions occurred.

PGE$_1$ also causes fewer local side effects than any other drug currently used for penile injection [10]. Intracavernous injection of vasoactive agents in the rabbit, including phenoxybenzamine, papaverine, phentolamine and PGE$_1$, has shown surprising differences in the effects of these substances on penile tissue [16]. Phenoxybenzamine caused severe inflammation and sclerosis of the corpus cavernosum and papaverine caused mild inflammation, but with PGE$_1$ neither inflammatory nor fibrotic reactions were observed. Subsequently, Aboseif et al. [1] studied the effect of repeated penile injections on semian penile tissue. With papaverine they found a loss of intracavernous architecture after 75 injections; a similar number of injections of PGE$_1$ resulted only in smooth-muscle hypertrophy.

Repeated injection of papaverine and/or phentolamine has caused fibrosis and/or angulation of the penis in humans. Experimental data have shown that this penile tissue damage results from the properties of the drug itself [16, 17]. The papaverine/phentolamine combination has been shown to precipitate at a pH of > 5.0 [14]; because the pH of blood is > 7.0, this may cause primary intracorporal scarring. However, in our series, even after as many as 400 PGE$_1$ injections in a single individual, no evidence of penile fibrosis or angulation occurred. A larger series is necessary for confirmation of the absence of long-term detrimental effects on penile tissue. Of the potential short-term side effects caused by intracavernous injections, priapism is the most worrisome. Not only is the patient distressed and in pain, but tissue ischemia can result in permanent penile injury. In our limited experience with papaverine, we found that its therapeutic range is small and that there is no linear correlation between the dose and the duration of erection. Therefore, patients in an auto-injection program might easily exceed the therapeutic dose and run the risk of priapism. None of our PGE$_1$ patients selected for auto-injection experienced a painful prolonged erection that required treatment after injection. The linear correlation between dose and duration of erection enables the patient to vary the dose, depending on his sexual desire.

Of our patients with neurogenic impotence, five developed an erection lasting 5–7 h after the injection of the 20-μg PGE$_1$ test dose. Although this erection was not painful and disappeared without treatment, we recommend that for patients with neurogenic impotence, the test dose should be reduced to 10 μg. Nevertheless, one patient developed a priapism that lasted 48 h after receiving an injection of 10 μg PGE$_1$; he finally received a penile prosthesis. Therefore, all patients are carefully instructed to return to their physician if the erection should last longer than 5 h.