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ABSTRACT

Recent human and animal studies have shown a possible role for calcitonin gene-related peptide in penile erection and a therapeutic benefit in combination with prostaglandin E1 for autoinjection therapy. The ethical committee approved calcitonin gene-related peptide-prostaglandin E1 combination for cases of nonresponse or cavernous fibrosis to papaverine-phentolamine. Since June 1990, 65 patients (59 nonresponders and 6 with fibrosis) were injected with 5 μg calcitonin gene-related peptide plus 10 μg prostaglandin E1. Of the 59 nonresponders to papaverine-phentolamine 31 and of the 6 patients with fibrosis 5 had full erectile response. Of these 36 patients 2 experienced pain during the pharmacologically induced erection. A total of 39 patients who had had at least 20 autoinjections of calcitonin gene-related peptide plus prostaglandin E1 was available for minimum followup. There were no side effects, such as pain (the 2 patients with pain mentioned previously were not included in the autoinjection therapy group), systemic side effects or (increased) fibrosis. Our results show that a combination of calcitonin gene-related peptide and prostaglandin E1 may be beneficial to the treatment of impotence in carefully selected patients.

KEY WORDS: impotence, penile erection, prostaglandins E, calcitonin gene-related peptide

Since the identification of the neurotransmitters for penile erection would have significant impact on the treatment of erectile dysfunction, research has focused on this topic of pharmacological-mechanical coupling during the last several years. Recently, endothelial derived relaxing factor has been shown to participate in cavernous smooth muscle relaxation. The classical drugs (papaverine, papaverine plus phentolamine and prostaglandin E1) for autoinjection therapy induce a full erectile response in about 50 to 70% of an unselected population of men with erectile dysfunction. The remaining patients with erectile dysfunction cannot be treated by autoinjection, although they would fit into its selection criteria and be willing to accept this therapeutic option. Therefore, a new drug for intracavernous injection with a higher response rate is needed, at least for the latter patients. Previous studies have shown the combination of prostaglandin E1 with calcitonin gene-related peptide for intracavernous injection to be more effective in inducing an erectile response than papaverine plus phentolamine or prostaglandin E1 alone. Therefore, we offered patients not responding to papaverine plus phentolamine with a sufficient erectile response or those with cavernous fibrosis during such therapy a combination of 5 μg calcitonin gene-related peptide plus 10 μg prostaglandin E1. Our followup data are reported.

PATIENTS AND METHODS

At our impotence clinic all patients undergo a comprehensive noninvasive or semi-invasive diagnostic evaluation. Since we routinely use intracavernous injections of vasoactive drugs for this evaluation, patients with stages III and IV arterial occlusive disease, cardiac dysrhythmias, recent myocardial infarction, sexual deviation, severe psychogenic disorders, addiction, severe liver insufficiency and age older than 65 years were excluded. Case history including a questionnaire and sexual case history by a psychiatrist were taken. Blood laboratory tests, pharmacological tests, single potential analysis of cavernous electric activity and Doppler study were performed. Pharmacological testing was done in a relaxed atmosphere and a urologist based on inspection and palpation, and graded as follows: E0—no response, E1—slight tumescence, E2—medium tumescence, E3—full tumescence, E4—full tumescence with medium rigidity and E5—full erection.

When the high dose of papaverine-phentolamine plus stimulation did not induce an erectile response sufficient for intercourse, the patients were informed about the high likelihood of venous leakage as the etiology of the erectile dysfunction, and the therapeutic options of venous surgery, penile prosthesis and a trial of calcitonin gene-related peptide plus prostaglandin E1 were presented. Marked cavernous fibrosis due to autoinjection therapy with other drugs was the other indication for the combination was approved by the Ethical Committee of the Medizinische Hochschule Hannover (approval No. 32). The patients were extensively informed about the experimental nature of this drug combination and possible side effects, such as severe circulatory symptoms or significant cavernous fibrosis. They were told that the intracavernous injection of 1 compound (prostaglandin E1) alone may be tried but the outcome would probably be less effective.

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related peptide plus 10 μg. prostaglandin E1 intracavernously in the supine position without any stimulation. When this dose did not induce a full erectile response, the same amount was injected with additional stimulation after a delay of at least 24 hours. If the calcitonin gene-related peptide-prostaglandin E1 mixture induced an erection sufficient for intercourse, the patients were trained in the handling of the procedure itself and advised to present immediately if a side effect occurred. Due to the experimental nature of the study, follow-up was done after every 10 autoinjections, and it included specific case history, physical examination, blood pressure measurement and blood laboratory tests. When cavernous fibrosis was suspected by case history or physical examination, high resolution sonography was performed to examine the cavernous bodies.

RESULTS

From September 1988 to May 1992, 59 patients with an insufficient erectile response to 30 mg. papaverine plus 1 mg. phentolamine and stimulation, and 6 with cavernous fibrosis due to autoinjection therapy with papaverine-phentolamine selected the calcitonin gene-related peptide plus prostaglandin E1 combination to restore erectile potency. Of the 59 nonresponders to papaverine-phentolamine 33 achieved a full erection (E5), 21 an almost full erection (E4) and 5 tumescence (E2 or E3) with calcitonin gene-related peptide-prostaglandin E1. Two patients with a full erectile response experienced intra- penile pain but there were no other acute objective or subjective side effects. Of the 6 patients with cavernous fibrosis calcitonin gene-related peptide-prostaglandin E1 induced a full erection (E5) in 5 and medium erection (E3) in 1. No acute side effects were observed in this group.

Due to the inconvenience of the intracavernous injection itself, the insufficient erectile response or the unknown long-term effects of this study only 34 of the 59 nonresponders and 5 of the 6 patients with fibrosis entered the autoinjection program with calcitonin gene-related peptide plus prostaglandin E1. Of 26 patients who completed at least 20 autoinjections 17 had done more than 40 and 9 had done more than 80 injections. No cavernous fibrosis or penile deviation was found subjectively or objectively (palpation) in any of the nonresponders, nor was there any increase in size of the fibrous area (5 patients) or of the penile deviation (2 patients) in the fibrosis group. There were no significant changes in blood laboratory tests and prolonged erections (duration more than 6 hours).

DISCUSSION

Previous studies have shown the combination of calcitonin gene-related peptide and prostaglandin E1 to be more effective in inducing a full erectile response than the combination of papaverine-phentolamine or prostaglandin E1 alone. In our series the combination of 5 μg. calcitonin gene-related peptide and 10 μg prostaglandin E1 induced a full erectile response in 31 of 59 patients (53%) who had had an insufficient response to papaverine-phentolamine. Although we know that prostaglandin E is somewhat more effective in inducing a full erectile response, we did not routinely inject intracavernously prostaglandin E1 alone, since the combination of calcitonin gene-related peptide plus prostaglandin E1 appeared to be significantly more effective. This practice is also supported by the 53% rate if full erections with calcitonin gene-related peptide plus prostaglandin E1 in patients who did not respond to papaverine plus phentolamine. This assumption is in accordance with the findings of another group working with the combination of calcitonin gene-related peptide plus prostaglandin E1 but it was used only in patients not responding to 80 mg. papaverine plus 2 mg. phentolamine or to 40 μg. prostaglandin E, with a reported success rate of 25%. The superior effectiveness of the combination of calcitonin gene-related peptide plus prostaglandin E1 compared to prostaglandin E1 alone, although he amount of prostaglandin E1 in the combination is reduced, may be explained by the different effector mechanisms of these substances. Prostaglandin E1 acts via specific receptors on the cell surface, whereas calcitonin gene-related peptide relaxes smooth muscles by hyperpolarization, most likely induced by potassium channel opening. Furthermore, calcitonin gene-related peptide seems to stimulate the production of cyclic adenosine monophosphate, resulting in smooth muscle relaxation.

In addition to the potentiation effect of the combination of calcitonin gene-related peptide plus prostaglandin E1 regarding erectile response, a pain reducing effect of the combination compared to prostaglandin E1 alone has been described previously. This low rate of pain during and/or after the intracavernous injection was reproduced in our series with only 2 of 65 patients (3%) experiencing pain after the injection of the combination of calcitonin gene-related peptide plus prostaglandin E1. This 3% rate is significantly lower than the 20 to 30% rate after prostaglandin E1 alone. The pain reducing effect of the combination of calcitonin gene-related peptide plus prostaglandin E1 may be due to the reduction of the amount of prostaglandin E1 in the combination compared to the application of prostaglandin E1 alone, as well as the anti-inflammatory effect of calcitonin gene-related peptide itself.

The results of this clinical experimental study on patients with erectile dysfunction who are either not responding to papaverine-phentolamine or in whom cavernous fibrosis develops due to papaverine-phentolamine suggest a possible beneficial effect of the combination of calcitonin gene-related peptide plus prostaglandin E1 for intracavernous injection. Because of the experimental nature of our study patients should be carefully selected and followed closely.

REFERENCES


