ROLE OF THE NITRIC OXIDE DONOR LINSIDOMINE CHLORHYDRATE (SIN-1) IN THE DIAGNOSIS AND TREATMENT OF ERECTILE DYSFUNCTION*

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ABSTRACT—**Objectives.** Recently, nitric oxide was shown to be a mediator of penile erection in men and the nitric oxide donor linsidomine chlorhydrate (SIN-1) was introduced as a novel treatment option in patients with erectile dysfunction. We now present our follow-up results with the intracavernous application of SIN-1.

Methods. One hundred thirteen patients with erectile dysfunction of various etiologies and 10 normal control subjects underwent intracavernous pharmacotesting with 1 mg SIN-1. Of the 113 patients, 71 (62.8%) underwent additional pharmacotesting with a mixture of papaverine (15 mg/mL) and phentolamine (0.5 mg/mL) (P/P). Forty-eight responders to SIN-1 were enrolled in an autoinjection program with this substance.

Results. All normal control subjects had full rigid erections lasting 40 to 70 minutes. Of 113 patients, 78 (69%) had responses sufficient for intercourse with SIN-1, and the other 35 patients (31%) demonstrated inadequate responses. All 44 responders to SIN-1 who also received P/P had erections sufficient for intercourse with P/P in doses of 0.25 to 2 mL (mean, 0.6 ± 0.3 mL). Six patients (13.6%) had prolonged erections with minimal to moderate doses of P/P. From the total of 27 patients who had erections insufficient for intercourse with SIN-1, 20 (74.1%) had good responses with 0.25 to 2.0 mL P/P (mean, 1.5 ± 0.5 mL). One patient (4%) had a prolonged erection with 1.0 mL P/P. After 10 to 150 injections/patient (total of 1160 injections; mean, 24.1 injections), no significant side effects were noted with SIN-1.

Conclusions. Our data suggest that intracavernous SIN-1 is safe and efficacious in the majority of patients with erectile dysfunction; however, it has a lower smooth muscle relaxing effect than a combination of P/P. The absence of severe side effects, including priapisms, may be explained by the use of a physiologic pathway for induction of the erectile response and the rapid intracavernous decomposition of SIN-1.

Penile erection requires a series of events that includes cavernous and vascular smooth muscle relaxation, increased arterial inflow, and subsequent venous outflow restriction. Recent work suggests that the initial step, cavernous and vascular smooth muscle relaxation, is mediated by the synthesis and release of nitric oxide from nerves innervating vascular and cavernous smooth muscles.[1-4] Therefore, the use of the L-arginine/nitric oxide pathway seems to be a possible approach in the treatment of erectile dysfunction. Linsidomine chlorhydrate (SIN-1; Corvasal Intracoronaire, Hoechst, France), the active hepatic metabolite of

*Supported by grants from Deutsche Forschungsgemeinschaft Stie 96/2-2 and Tru 343/1-1.
Submitted: February 21, 1994, accepted (with revisions): May 19, 1994

molsidomine (N-ethoxycarbomyl-3-morpholinosydninimine), is believed to liberate nitric oxide nonenzymatically (nitric oxide donor). Theoretically, a nitric oxide donor may be superior to other vasoactive drugs because it may resemble more closely the physiologic sequence of events in penile erection. Our preliminary results with the intracavernous application of SIN-1 suggested a possible role in the treatment of patients with erectile dysfunction.[5] We now report our extended follow-up with SIN-1 in the diagnosis and treatment of patients with erectile dysfunction.

MATERIAL AND METHODS

All patients underwent a comprehensive and standardized workup for erectile dysfunction, including a detailed case history, physical examination, sexual case history (questionnaire), routine blood tests, pharmaco-Doppler ultrasound, corpus cavernosum electromyogram,[6] and pharmacotesting. When indicated, pharmacocavernosometry and pharmacocavernography were carried out (12 patients).

All 113 patients (8 patients with primary and 105 patients with secondary impotence) and 10 normal control subjects received 1 mg SIN-1 intracavernously. Of 113 patients, 71 (62.8%) received additional, at least three, injections of a mixture of papaverine (15 mg/mL) and phentolamine (0.5 mg/mL) (P/P) prior to pharmacotesting with SIN-1. Increasing doses of 0.25 to 2.0 mL were given according to the erectile response. All injections were given in a supine position. Responses to P/P and SIN-1 were evaluated by a urologist after 10, 20, and 30 minutes by inspection and palpation and graded as follows: E 0, no response; E 1, slight tumescence; E 2, medium tumescence; E 3, full tumescence but no rigidity; E 4, full tumescence with medium rigidity, sufficient for intercourse; E 5, full rigid erection. Forty-eight SIN-1 responders entered an autoinjection program with SIN-1. All patients were seen as outpatients after the first 10 injections and thereafter following each series of 25 injections. At follow-up visits, a history and physical examination and routine blood tests were taken.

All patients as well as the normal control subjects were extensively informed of the study and the possible side effects (prolonged erections, cavernous fibrosis, infection, cavernous necrosis, and systemic side effects such as hypotension). Written consent was obtained from all participants. The study was approved by the Ethics Committee of the Medizinische Hochschule Hannover.

RESULTS

The mean patient age was 48.9 ± 11.9 years. Erectile dysfunction was prevalent for 56 ± 27.9 months. The mean age of the volunteers (control subjects with normal erectile function) was 34 ± 8.4 years. The patients' past medical histories included nicotine abuse (25 patients), peripheral vascular disease (21 patients), hypertension (17 patients), diabetes (17 patients), hyperlipidemia (12 patients), pelvic trauma (9 patients), and alcohol abuse (6 patients). In 27 patients the medical history was not contributory.

Following intracavernous administration of SIN-1, all normal control subjects had full rigid erections (E 5) lasting 40 to 70 minutes, which spontaneously resolved. No complications or side effects such as penile pain, hemorrhage, infection, or prolonged erections occurred. Of the patients with erectile dysfunction, 40 had E 5, 38 had E 4, 20 had E 3, 14 had E 2, and 1 had E 1 responses to intracavernous SIN-1 pharmacotesting. Again, no side effects were noted.

Electromyographic patterns in patients responding with E 4 and E 5 erections to SIN-1 (32 normal, 40 pathologic) did not differ significantly from patients responding with E 1 to E 3 erections (18 normal, 23 pathologic). With respect to risk factors, no differences were found between responders and nonresponders except in patients following pelvic trauma and patients with primary erectile dysfunction. All 9 patients after pelvic trauma (mean age, 30.8 ± 6.2 years) and all 8 patients with primary erectile dysfunction (mean age, 35.6 ± 9.6 years) responded to SIN-1 with E 4 or E 5 erections. Nine of 12 patients (75%) who underwent pharmacocavernosometry and pharmacocavernography for suspected venous leakage did not achieve erections sufficient for intercourse (E 1 to E 3; mean age, 56.3 ± 7.6 years).

Of 113 patients, 71 (62.8%) also underwent pharmacotesting with increasing doses of a mixture of papaverine (15 mg/mL) and phentolamine (0.5 mg/mL). Of these 71 patients, 64 (90.1%) had E 4 or E 5 erections, including all patients who showed adequate response to SIN-1 and 20 of 27 patients (74.1%) who failed. Mean doses of P/P in responders and nonresponders to SIN-1 were 0.6 ± 0.3 and 1.5 ± 0.5 mL, respectively ($p < 0.0001$, Student's t test). Of 44 SIN-1 responders, 6 (13.6%) and 1 of 27 SIN-1 nonresponders (4%) experienced prolonged erections for more than 240 minutes with P/P.

The 48 SIN-1 responders performed a total of 1160 self-injections (10 to 150 injections/patient, mean, 24.1). No complications such as penile pain,

fibrosis, infection, or prolonged erections were noted. All patients with the exception of 3 (93.75%) were satisfied with their response to SIN-1. Three patients withdrew from the study because the quality of the erectile responses to SIN-1 decreased.

COMMENT

Recently, nitric oxide has been identified as a mediator of cavernous smooth muscle relaxation and penile erection in vitro and in vivo.[1-4] Nitric oxide is synthesized from L-arginine by nitric oxide synthase (NOS); it acts on guanylate cyclase activation, which subsequently leads to an intracellular increase of cyclic guanosine 3',5' monophosphate (cGMP).[1] The intracellular receptor for cGMP is cGMP dependent protein kinase G, which is believed to phosphorylate ion channels, causing intracellular calcium depletion and smooth muscle relaxation. SIN-1 is a drug approved for the treatment of coronary spasms and for angiography of coronary arteries. It is believed to liberate nitric oxide nonenzymatically. The recommended dosage for angiography is 0.4 to 1 mg. Since our initial data showed a dose-dependent response to SIN-1 with more favorable results with 1 mg, all subsequent patients received 1 mg.[5]

In our present series 35 of 113 patients (31%) failed to respond with erections sufficient for intercourse. In our initial report[5] only 21% failed; thus, our present data are somewhat less favorable. This may be attributed to the higher percentage of patients with assumed neurogenic erectile dysfunction in our first 63 patients, since patients with predominantly neurogenic impotence, that is, diabetics and patients after pelvic trauma, tend to respond better to intracavernous pharmacotherapy.[7]

The fact that nonresponders to SIN-1 showed a tendency toward multiple risk factors and 20 of 27 nonresponders (74.1%) achieved erections sufficient for intercourse with P/P indicates that P/P may be preferable to SIN-1 in patients with a multifactorial origin of erectile dysfunction, that is, patients with significant arterial vascular disease and diabetic neuropathy. The higher smooth muscle relaxing potential of P/P is also reflected by the fact that SIN-1 nonresponders needed a significantly larger dosage of P/P than nonresponders to induce an erection sufficient for intercourse (1.5 ± 0.5 vs 0.6 ± 0.3 mL; $p < 0.0001$). Our observation that SIN-1 is not effective in the majority of patients with venous leakage is in accordance with the findings of others.[8] If venous leakage is a symptom of incomplete cavernous relaxation, further support is given to the assumption that SIN-1 causes submaximum cavernous relaxation.[9] In contrast, SIN-1 gives excellent results in patients with (assumed) relatively intact cavernous tissue, that is, younger patients with primary erectile dysfunction and erectile dysfunction due to pelvic trauma.

In 6 of 44 SIN-1 responders (13.6%) prolonged erections were seen with P/P. In contrast, SIN-1 did not cause any prolonged erections, even in normal subjects and in patients who needed only minimum amounts of P/P. Therefore, we consider SIN-1 the drug of choice in patients with proven or suspected increased sensitivity to other vasoactive agents. In addition, SIN-1 may prove to be the drug of choice in other subgroups of patients in the future (ie, impotence after pelvic surgery). If SIN-1 fails to induce a satisfactory erectile response, other agents, such as P/P or prostaglandin E_1, should be administered. Possible explanations for the absent priapismogenic potential of SIN-1 may be a more physiologic induction of erection and the rapid local metabolism of nitric oxide.[10]

After up to 150 injections/patient, no cavernous fibrosis was noted; with respect to local side effects such as intrapenile discomfort or pain, SIN-1 compares favorably to prostaglandin E_1 and the combination of papaverine and phentolamine. With prostaglandin E_1 20% to 40% of patients experience penile pain and with P/P, although less intense, most patients report a slight burning sensation during administration.[11] With SIN-1, no patients reported such a discomfort, which may indicate that the substance is well tolerated by the cavernous tissue. This is also supported by the fact that no inflammatory or fibrous reactions were seen after multiple intracavernous injections in the rabbit model.[12]

Currently, all patients at our institution undergoing intracavernous pharmacotesting receive 1 mg SIN-1. In case of a satisfactory erectile response, all patients are counseled to enter a self-injection program with SIN-1 for a maximum reduction of possible side effects. Patients not responding to SIN-1 are advised to undergo pharmacotesting with increasing doses of papaverine plus phentolamine. Responders continue with this regimen, whereas nonresponders are offered a trial with intracavernous calcitonin gene-related peptide plus prostaglandin E_1, since this combination was shown to be effective in the majority of P/P nonresponders.[13]

In conclusion, our data suggest that intracavernous SIN-1 is safe and efficacious in the majority of patients with erectile dysfunction; however, it has a lower smooth muscle relaxing potential than a combination of papaverine and phentolamine.

The fact that no prolonged erections were seen even in patients with a past history of priapisms may be explained by the more physiologic induction of erection with a nitric oxide donor and a rapid intracavernous decomposition of SIN-1.

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ACKNOWLEDGMENT. To Nicola van Dornick for review of the linguistic style.

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