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PRELIMINARY RESULTS WITH THE NITRIC OXIDE DONOR LINSIDOMINE CHLORHYDRATE IN THE TREATMENT OF HUMAN ERECTILE DYSFUNCTION

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ABSTRACT

Recent experimental studies showed an important role of endothelium derived relaxing factor for cavernous smooth muscle relaxation. Since nitric oxide seems to account for the biological actions of endothelium derived relaxing factor, a study was done to examine a possible role of the nitric oxide donor linsidomine chlorhydrate (SIN-1) in the treatment of erectile dysfunction.

To determine a therapeutically useful dose 0.1, 0.2, 0.5 and 1 mg. SIN-1 were injected intracavernously in patients with erectile dysfunction. Each dose was given to 2 patients. Then, 63 patients received 1 mg. SIN-1, including 7 who had prolonged erections to minimal doses of papaverine plus phentolamine and 4 who did not respond with a full erection to other pharmacological agents. Intracavernous injection of SIN-1 induced a dose-dependent erectile response by increasing the arterial inflow and relaxing cavernous smooth muscles. Of the patients 29 had a full, 21 an almost full and 13 a moderate erection to 1 mg. SIN-1. There were no systemic or local side effects. In the patients with prolonged erections to papaverine plus phentolamine the mean duration of a full erectile response to SIN-1 was 57 minutes. Compared to the responses to a papaverine (15 mg./ml.) and phentolamine (0.5 mg./ml.) mixture, the erection induced by SIN-1 was superior in 10, comparable in 47 and inferior in 6 patients.

Our data suggest a possible role for SIN-1 in the treatment of erectile dysfunction. Possible advantages may be that erection is induced by a mechanism similar to that occurring physiologically, a decreased risk of inducing prolonged erections and low therapy costs.

KEY WORDS: penile erection, impotence, nitric oxide

Cavernous smooth muscles have a crucial role in penile erection. Relaxation of the arterial and sinusoidal cavernous smooth muscles induces an erection by decreasing peripheral resistance, entrapping blood within the sinusoids and restricting cavernous outflow.[1] In vascular smooth muscle endothelium derived relaxing factor is an important physiological mechanism for relaxation.[2] The current view is that nitric oxide or a nitric oxide-containing compound, synthetized from L-arginine, accounts for the biological actions of endothelium derived relaxing factor.[3] Recent in vitro studies on rabbit and human penile tissues have shown that nitric oxide or a nitric oxide-containing compound, probably released from nerves, has a role in the regulation of cavernous smooth muscle tone.[4-7] In vivo studies in rabbits further support a role for the L-arginine/nitric oxide pathway in penile erection.[8]

These experimental data suggest that in the treatment of erectile dysfunction use of the L-arginine/nitric oxide pathway may be an interesting approach, since it would resemble the physiological sequence of events in erection. Linsidomine chlorhydrate (SIN-1) is the active metabolite of the antianginal drug molsidomine[9] (N-ethoxycarbonyl-3-morpholino-sydnonimine) and it is believed to liberate nitric oxide nonenzymatically (nitric oxide donor). Preliminary results showed that SIN-1 produces an erection in patients with erectile dysfunction.[10] We examined the effects of intracavernous application of SIN-1 in 63 men with erectile dysfunction, and evaluated its possible therapeutic potential in the treatment of erectile dysfunction.

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PATIENTS AND METHODS

SIN-1 was injected intracavernously in 63 patients from our impotence clinic. Before entering the study the patients underwent a comprehensive evaluation regarding the etiology of the erectile dysfunction, including case history, physical examination, sexual case history (by a psychiatrist), blood laboratory studies, pharmaco-Doppler ultrasound, single potential analysis of cavernous electrical activity evaluation[11] and pharmacological testing.[12] When indicated by case history or the aforementioned examinations,[12] pharmaco-angiography or cavernosometry was done. In case the standardized medication of 15 mg./ml. papaverine and 0.5 mg./ml. phentolamine, with a maximal dose of 3 ml., did not induce a full erection (at least 3 intracavernous injections were done), prostaglandin E1 (maximal dose 40 μg.) was applied. In case of incomplete erection to prostaglandin E1 a combination of 10 μg. prostaglandin E1 and 5 μg. calcitonin gene-related peptide[13] was tried. All injections were done with the patient in the supine position. Only 1 dose a day was injected. To enhance reproducibility the patients were advised to restrain from psychogenic or reflexogenic stimulation. The erectile response was evaluated by a urologist 10, 20 and 30 minutes after the injection.

After the diagnostic evaluation all patients were injected with SIN-1 intracavernously. Before the injection the patients were extensively informed about the study and about possible side effects (prolonged erections, systemic side effects, such as decreased blood pressure with unconsciousness, cavernous fibrosis and infection). After the explanation written consent was obtained from each patient. The study was approved by the Ethics Committee of the University of Hannover (approval No. 532).

SIN-1 is officially approved for treatment of coronary spasms

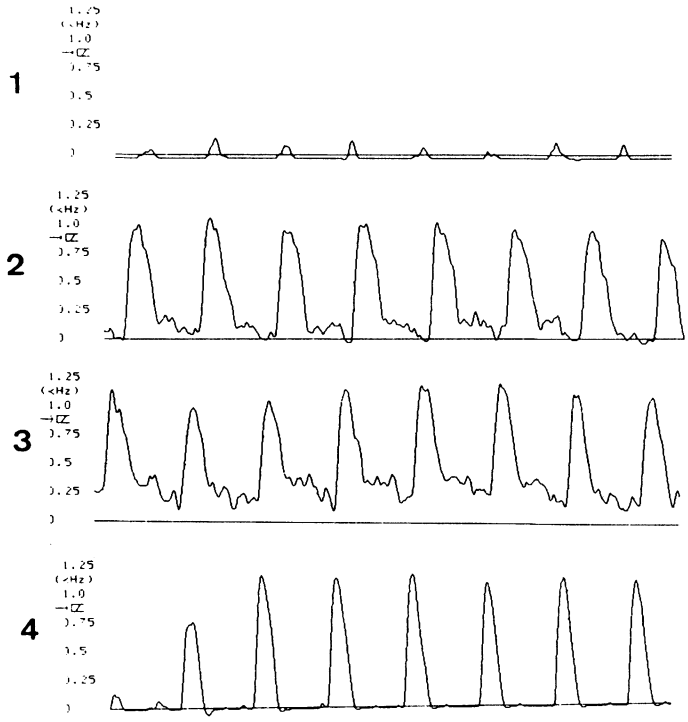

FIG. 1. Intracavernous injection of 0.5 mg. SIN-1 in 51-year-old patient with venogenic and arteriogenic erectile dysfunction induced significant increase in penile arterial blood flow velocity during 140 minutes (continuous wave Doppler ultrasound, 8 MHz. probe). *1*, Doppler signals before SIN-1. *2*, 3 minutes after intracavernous injection of 0.5 mg. SIN-1 (E1). *3*, 10 minutes after SIN-1 (E2). *4*, 35 minutes after SIN-1 (E4).

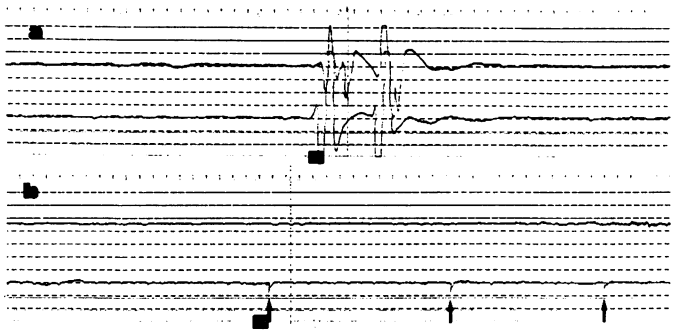

FIG. 2. Recording of cavernous electric activity (frequency range 0.5 to 500 Hz.) with 2 needle electrodes, 1 in each corpus, in 39-year-old patient with erectile dysfunction, negative organic findings and high probability of psychogenic etiology. *a*, upper recording shows normal electric activity in flaccid state (recorded during 40 minutes), synchronous in both cavernous bodies with upper tracing in right and lower in left cavernous body. *b*, 20 seconds after intracavernous injection of 1 mg. SIN-1. Lower recording shows dramatically reduced cavernous electric activity in both cavernous bodies, with only short lasting potentials of low amplitude (arrows) in left corpus. This reduced cavernous electric activity lasted more than 60 minutes (end of registration).

and for angiography of the coronary arteries. The dosage recommended by the manufacturer is 0.4 to 1 mg. Therefore, we applied 0.1 mg. in 2 patients, 0.2 mg. in 2 and 0.5 mg. in 2. Since a main purpose of this study was to evaluate a therapeutically useful dose, considering effect versus possible side effects, such as pain, prolonged erections and systemic reactions, all patients (including the aforementioned 6) received 1 mg. Nine patients were also given 2 mg. SIN-1, since 1 mg. induced only an insufficient (less than category E5) erectile response. In 6 of these 9 patients SIN-1 was considered the last therapeutic alternative regarding available drugs for autoinjection therapy. Since a possible therapeutic use of SIN-1 was to be evaluated, patients receiving 2 mg. SIN-1 were advised to use additional reflexogenic and/or psychogenic stimulation to improve the erectile response. The first 2 of these 9 patients were medical doctors. Before the injection all patients receiving 2 mg. SIN-1 were informed about the unusually high dose with possible severe systemic side effects (hypotension and hypovolemic shock). The local response to SIN-1 was measured by inspection and palpation by a urologist; the erectile response was classified into 6 categories: E0—no response, E1—minimum tumescence, E2—medium tumescence, E3—full tumescence without rigidity, E4—full tumescence with medium rigidity and E5—full erection. Bidirectional Doppler sonography of the 4 penile arteries was done in the first 6 injections, 2 patients each receiving 0.1, 0.2 and 0.5 mg. SIN-1. Single potential analysis of cavernous electrical activity was done in 2 patients receiving 1 mg. SIN-1. Pulse and blood pressure were closely monitored in the first 8 patients. During the entire procedure the patient was in the supine position.

RESULTS

At the dosages used intracavernous application of SIN-1 induced an erectile response in all patients. The erectile response, measured by tumescence and rigidity, as well as by arterial flow velocity, was dose-dependent. Intracavernous injection of 0.1 mg. SIN-1 (2 patients) induced a medium tumescence without rigidity (E2) after a mean of 15 minutes and lasting for 45 minutes. By Doppler sonography a significant increase in cavernous arterial flow was observed for a mean of 85 minutes. Intracavernous injection of 0.2 mg. SIN-1 (2 patients) induced an almost full erection (E4 to E5) for 40 minutes and a significant increase in arterial flow was observed for 135 minutes. Intracavernous injection of 0.5 mg. SIN-1 (2 patients) induced a full erection (E5) in 1 patient for 40 minutes and full tumescence with medium rigidity (E4) in 1, and an increase in arterial inflow was observed for a mean of 150 minutes (fig. 1). Recording of cavernous electrical activity showed disappearance of the potentials about 20 seconds after the intracavernous injection of 1 mg. SIN-1 in both patients (fig. 2). Intracavernous injection of 1 mg. SIN-1 was done in 63 patients and induced a full erection (E5) in 29, full tumescence with medium rigidity (E4) in 21 and full tumescence (E3) in 13.

In 9 of the patients with an incomplete erectile response (E3) to 1 mg. SIN-1 pharmacocavernosometry showed venous leakage. These patients were injected with 2 mg. SIN-1. Among the 9 patients who received intracavernous injection of 2 mg. SIN-1 an almost full erection (E4 to E5) was observed in 4, while 5 achieved an erectile response (E4) comparable to that obtained with 1 mg. SIN-1. All 4 patients with an almost full erection after 2 mg. SIN-1 achieved a full erection (E5) with additional stimulation. Comparing the maximal erectile response to SIN-1 to that of the combination of papaverine and phentolamine, SIN-1 was superior in 10 of the 63 patients, comparable in 47 and inferior in 6.

In 2 of 4 patients with insufficient erectile response to maximal doses of papaverine (45 mg.) plus phentolamine (1.5 mg.), prostaglandin E1 (40 μg.) and the combination of prostaglandin E1 (10 μg.) plus calcitonin gene-related peptide (5 μg.)[14] intracavernous injection of 2 mg. SIN-1 induced an almost full erection (E4 to E5), which became a full erection with additional stimulation. Both patients are currently on SIN-1 autoinjection therapy.

A total of 4 patients did not respond to maximal doses of papaverine plus phentolamine or prostaglandin E1 with a full erection. The combination of 10 μg. prostaglandin E1 plus 5 μg. calcitonin gene-related peptide induced a full erection (E5) for 60 minutes. In these patients intracavernous injection of 1 mg. SIN-1 induced only an incomplete erectile response (E3 or E4). In 2 other patients responding better to the papaverine-

phentolamine combination the diagnostic evaluation was highly suspicious for pure psychogenic impotence.

A total of 7 patients showed a pure neurogenic etiology for the erectile dysfunction on diagnostic evaluation. A dosage of 1 mg. SIN-1 was injected into 6 patients with long lasting full erections to relatively small doses of the combination of papaverine and phentolamine. With a mean dose of 0.33 ml. (5 mg. papaverine and 0.16 mg. phentolamine) 4 of the 6 men had a mean full erectile duration of 230 minutes; 2 of them presented with 2 episodes of prolonged erection. Another patient was transferred to us because multiple prolonged erections developed of about 40 hours to doses of 20 mg. papaverine. In these 7 patients intracavernous injection of 1 mg. SIN-1 induced a full erection lasting for 40 to 90 minutes (mean 57 minutes).

In all but 1 patient the injection of SIN-1 induced no objective or subjective systemic side effects. One patient reported sweating after intracavernous injection of 2 mg. SIN-1. No patient reported pain or burning during or after the intracavernous injection of SIN-1. Of the patients who were on papaverine and phentolamine autoinjections 4 noticed subjectively that intracavernous application of SIN-1 was much more comfortable than injection of the papaverine-phentolamine mixture.

DISCUSSION

Our study shows that the intracavernous injection of SIN-1 induces a dose-dependent erectile response. By Doppler sonography we could demonstrate that this erectile response is accompanied by a dramatic increase in cavernous arterial blood flow. In vitro studies showed cavernous smooth muscle relaxation to SIN-1.[7] These findings are in agreement with our recordings of cavernous electrical activity before and after intracavernous injection of SIN-1. We found an almost complete disappearance of cavernous electrical activity after SIN-1, which shows that the erectile response to intracavernous SIN-1 is due to cavernous smooth muscle relaxation.[11]

Comparing the maximal erectile responses, the erection induced by SIN-1 was superior to that produced by the combination of papaverine and phentolamine in 10 of 63 patients, comparable in 47 patients and inferior in 6. The mechanisms behind the effects of the combination are complex, and probably not only include the phosphodiesterase inhibiting effects of papaverine and the α-adrenoreceptor blocking effect of phentolamine but additional actions. SIN-1 is believed to liberate nitric oxide nonenzymatically, which, in turn, stimulates guanylate cyclase leading to an increase in the intracellular concentration of cyclic guanosine 3′, 5′ monophosphate. SIN-1 also hyperpolarizes the cell membrane by influencing the sodium-potassium pump,[14] thus rendering the smooth muscle cell less responsive to adrenergically mediated contraction. The actions of the papaverine-phentolamine combination and of SIN-1 are not dependent on an intact endothelium, which should make both alternatives effective also in cases when the erectile dysfunction may be due to endothelial malfunction, such as in diabetes mellitus or hypercholesterolemia.[15-17] Our series suggests SIN-1 to be comparable or even superior to the combination of papaverine and phentolamine. However, controlled comparative studies are needed to strengthen these assumptions. Furthermore, the reasons for possible differences in efficacy remain to be established.

In 4 of 63 patients who received SIN-1 neither 45 mg. papaverine plus 1.5 mg. phentolamine, 40 μg. prostaglandin E1 nor 10 μg. prostaglandin E1 plus 5 μg. calcitonin gene-related peptide induced an erectile response allowing intercourse (even with additional stimulation). In 2 of these 4 patients intracavernous injection of SIN-1 combined with stimulation induced a full erection, thus enabling the patients to have intercourse without the insertion of a penile prosthesis or application of a vacuum device. We have no explanation for the apparent better efficacy of SIN-1 in these patients. It is known that the number of prostaglandin E1 receptors is reduced in several diseases, such as diabetes mellitus,[18] and that this may contribute to a lesser effect. In such cases SIN-1 may be an effective alternative.

A 1 mg. dose of SIN-1 was injected into 6 patients with long lasting full erections to small doses of the papaverine-phentolamine combination. History revealed a spinal cord injury (complete below T11) in 1 patient and a vertebral nucleus prolapse (L4/L5) in 1. In 4 patients abnormal single potential analysis of cavernous electrical activity findings was obtained, with the other examinations being normal. With a mean dose of 0.33 ml. (5 mg. papaverine and 0.16 mg. phentolamine) 4 of 6 men had a mean duration of a full erection of 230 minutes (2 of them presented with episodes of prolonged erections). One patient was transferred to us because of multiple prolonged erections about 40 hours in duration with doses of 20 mg. papaverine. The diagnostic constellation in these 7 patients is highly suggestive of pure neurogenic impotence. Although these patients are usually overreactive to intracavernous pharmacotherapy, intracavernous injection of 1 mg. SIN-1 induced a full erection lasting 40 to 90 minutes (mean 57 minutes). This finding may be explained by the local pharmacokinetics of SIN-1 and the rapid decomposition of nitric oxide within the cavernous tissue, which should prevent the occurrence of prolonged erections.

Most patients on autoinjection therapy with a papaverine-phentolamine mixture report a slight burning sensation at the injection site during injection of the drug mixture. No patient who received SIN-1 intracavernously reported any pain or burning sensation during or after the injection. This observation may further indicate the fact that SIN-1 is well tolerated by the cavernous tissue.

In animal studies[19] as well as at followup of patients on autoinjection therapy,[20] chronic intracavernous injection of papaverine has been shown to result in significant cavernous fibrosis. Chronic intracavernous injection of prostaglandin E1 seems to have less fibrotic potential on cavernous tissue, as shown in animal[19] and human studies.[20] Since SIN-1 is delivered as lyophilized powder to be dissolved in physiological (0.9%) saline solution, it should also have minor fibrotic effects on the cavernous tissue. Nevertheless, chronic animal studies are urgently needed to elucidate this important issue. Since therapy costs are of increasing importance in all countries, the cost of SIN-1 therapy is of interest (the prices indicated are those for Germany and France, respectively). The cost of 1 ampule of SIN-1 (1 mg. delivered lyophilized with 1 ampule 0.9% saline solution) equals approximately the cost of an ampule of papaverine (30 mg. in solution) and is approximately one-fifth of the cost of prostaglandin E1 (20 μg. lyophilized, delivered without solution for dissolution). Thus, SIN-1 seems to be an affordable alternative in the treatment of erectile dysfunction.

In conclusion, our preliminary results suggest that SIN-1 is an attractive option in the autoinjection therapy for erectile dysfunction. The absence of prolonged erections, the high effectiveness to induce a sufficient erectile response and the low cost indicate the potential of SIN-1 to become a standard drug for intracavernous injections. Before widespread use can be advocated, long-term animal studies must examine the local effect of this agent on the cavernous tissue.

REFERENCES

1. Lue, T. F. and Tanagho, E. A.: Physiology of erection and pharmacological management of impotence. J. Urol., **137:** 829, 1987.
2. Furchgott, R. F. and Zawadzki, J. V.: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature, **288:** 373, 1980.
3. Moncada, S., Palmer, R. M. J. and Higgs, E. A.: Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol. Rev., **43:** 109, 1991.

4. Ignarro, L. J., Bush, P. A., Buga, G. M., Wood, K. S., Fukuto, J. M. and Rajfer, J.: Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem. Biophys. Res. Comm., **170:** 843, 1990.
5. Holmquist, F., Hedlund, H. and Andersson, K.-E.: L-N^G-nitro arginine inhibits non-adrenergic, non-cholinergic relaxation of human isolated corpus cavernosum. Acta P'hysiol. Scand., **141:** 441, 1991.
6. Kim, N., Azadzoi, K. M., Goldstein, I. and de Tejada, S. I.: A nitric oxide-like factor mediates nonadrenergic noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. J. Clin. Invest., **88:** 112, 1991.
7. Holmquist, F., Hedlund, H. and Andersson, K. E.: Characterisation of inhibitory neurotransmission in the isolated corpus cavernosum from rabbit and man. J. Physiol., in press.
8. Holmquist, F., Stief, C. G., Jonas, U. and Andersson, K.-E.: Effects of the nitric oxide synthase inhibitor N^G-nitro-L-arginine on the erectile response to cavernous nerve stimulation in the rabbit. Acta Physiol. Scand., **143:** 299, 1991.
9. Reden, J.: Molsidomine. Blood Vessels, **27:** 282, 1990.
10. Stief, C. G., Holmquist, F., Allhoff, E. P., Andersson, K. E. and Jonas, U.: Preliminary report on the effect of the nitric oxide donor SIN-1 on human cavernous tissue in vivo. World J. Urol., **9:** 237, 1991.
11. Stief, C. G., Djamilian, M., Schaebsdau, F., Truss, M. C., Schlick, R., Abicht, J. H., Allhoff, E. P. and Jonas, U.: Single potential analysis of cavernous electric activity—a possible diagnosis of autonomic impotence. World J. Urol., **8:** 75, 1990.
12. Stief, C. G., Bähren, W., Gall, H. and Scherb, W.: Functional evaluation of penile hemodynamics. J. Urol., **139:** 734, 1988.
13. Stief, C. G., Wetterauer, U., Schaebsdau, F. H. and Jonas, U.: Calcitonin-gene-related peptide: a possible role in human penile erection and its therapeutical application in impotent patients. J. Urol., **146:** 1010, 1991.
14. Vanhoutte, P. M.: Vascular physiology: the end of the quest? Nature, **327:** 459, 1987.
15. Saenz de Tejada, I., Goldstein, I., Azadzoi, K., Krane, R. J. and Cohen, R. A.: Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. New Engl. J. Med., **320:** 1025, 1989.
16. Azadzoi, K. M. and Saenz de Tejada, I.: Inhibition of endothelium-dependent relaxation by hypercholesterolemia in rabbit corpus cavernosum smooth muscle. J. Urol., part 2, **145:** 230A, abstract 72, 1991.
17. Mersdorf, A., Goldsmith, P. C., Diederichs, W., Padula, C. A., Lue, T. F., Fishman, I. J. and Tanagho, E. A.: Ultrastructural changes in impotent penile tissue: a comparison of 65 patients. J. Urol., **145:** 749, 1991.
18. Aboseif, S., Riemer, K., Stackl, W., Lue, T. and Tanagho, E.: Quantification of prostaglandin E1 receptors in the cavernous tissue of humans, primates and canines. J. Urol., part 2, **145:** 230A, abstract 70, 1991.
19. Aboseif, S. R., Breza, J., Diederichs, W., Bosch, R., Benard, F., Stief, C. G., Lue, T. F. and Tanagho, E. A.: Effect of chronic intracavernous injection of papaverine and prostaglandin E1 on erectile tissue in monkeys. J. Urol., part 2, **139:** 257A, abstract 377, 1988.
20. Jünemann, K.-P. and Alken, P.: Pharmacotherapy of erectile dysfunction: a review. Int. J. Impotence Res., **1:** 71, 1989.