Oral Midodrine for Prostaglandin E1 Induced Priapism in Spinal Cord Injured Patients

Jean-Marc Soler, Jean-Gabriel Previnaire,* Roger Mieusset and Pierre Plante

From the Laboratoire d'urodynamique et de sexology, Centre Bouffard Vercelli (JMS), Cap Peyrefite, Cerbère, Centre Calvé, Fondation Hopale (JGP), Berck sur mer and Centre de Stérilité masculine (JMS, RM) and Service d'urologie (JMS, PP), Centre Hospitalier Universitaire Toulouse, Toulouse Cedex, France

Abbreviations and Acronyms

ASIA = American Spinal Injury Association
DBP = diastolic blood pressure
ICI = intracavernous injection
LMN = lower motor neuron
PGE1 = prostaglandin E1
SBP = systolic blood pressure
UMN = upper motor neuron

Submitted for publication November 24, 2008.
* Correspondence: Centre Calvé, Fondation Hopale, 62600 Berck sur mer, France (telephone: +00333.21.89.33.86; FAX: +00333.21.89.31.40; e-mail: previnjg@hopale.com).

Purpose: We evaluated midodrine as oral treatment for pharmacologically induced priapism in spinal cord injured patients.
Materials and Methods: From 2004 to 2007 we treated 354 spinal cord injured patients with intracavernous injection of prostaglandin E1 to induce erection. Prolonged erection or priapism occurred in 14 cases (1.3% of intracavernous injections). High blood pressure and bradycardia (autonomic dysreflexia) were noted in 2 tetraplegic cases. Except in 2 patients oral midodrine was used as the only therapeutic approach to this event because of its alpha stimulant properties.
Results: All patients returned to the flaccid penile state within 30 to 45 minutes after midodrine administration. Oral midodrine was well tolerated with few side effects and without increasing the incidence of autonomic dysreflexia. At 6 months complete erection could be again induced by intracavernous injection in all treated patients.
Conclusions: Midodrine administered orally is a simple and efficient treatment for the priapism induced by intracavernous injection of prostaglandin E1. It could be the first line therapeutic approach before more aggressive procedures.

Key Words: penis, midodrine, priapism, alprostadil, spinal cord injury

Erectile dysfunction induced by spinal cord lesions often implies a pharmacological solution with phosphodiesterase type 5 inhibitors or PGE1 as treatment. ICI of vasoactive substances may cause prolonged erection or priapism.[1–3] Priapism is a persistent penile erection greater than 4 hours in duration that is unrelated to sexual excitement.[4] Idiopathic priapism is uncommon after spinal cord injury. With ICI of vasoactive substances the incidence of ischemic priapism has highly increased. Invasive therapy with cavernous blood aspiration and irrigation, and/or alphamimetic drug ICI is recommended in such cases. Few oral treatments have been reported, most in small patient series.[2,5–8]

Midodrine is an alpha stimulant used for symptomatic orthostatic hypotension. It is fully licensed for this indication in many countries, including France and the United States, but not in the United Kingdom. In spinal cord injured patients midodrine has been used for orthostatic hypotension[9] and to resolve ejaculation disturbances.[10] We evaluated midodrine efficacy as treatment for induced priapism in spinal cord injured patients.

Three clinical aspects of priapism are known. Ischemic priapism with intracavernous hypoxia and acidosis may induce penile fibrosis, and secondary severe and permanent erectile dysfunction.[11] High flow priapism due to arteriovenous fistula usually devel-

0022-5347/09/1823-1096/0
THE JOURNAL OF UROLOGY®

Vol. 182, 1096-1100, September 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.05.009

ops after urethral or perineal trauma. Embolization is needed when spontaneous resolution does not occur. Stuttering priapism, which must be considered an ischemic event, sometimes requires long-term medication to decrease its frequency and duration.[4]

MATERIALS AND METHODS

From January 1, 2004 to March 2008 we treated 354 consecutive spinal cord injured patients for erectile dysfunction. All patients were evaluated with the same protocol. After neurological evaluation cases were classified according to ASIA score and perineal dysfunction type, including UMN in cases of an exaggerated perineal reflex due to a central lesion or LMN in cases of an abolished reflex. Medical history and previous treatment were also recorded, as was the type of erectile dysfunction. Urinalysis, bladder and renal ultrasound, and creatinine clearance were routinely done as initial evaluation in our spinal injured patients. Initial evaluation was done in a specifically designed room allowing intimacy for manual penile stimulation and, if desired, visual erotic stimulation.[10]

The pharmacological procedure was begun when spontaneous erection was insufficient in terms of rigidity or duration, or missing. PGE1 ICI was begun at 5 μg in high paraplegic or tetraplegic UMN cases, at 7.5 μg in other paraplegic UMN cases and at 10 μg in LMN cases. Using a 2.5 μg step the PGE1 dose could be increased up to 30 μg if necessary. In case of failure 10 to 40 mg papaverine were added at 10 mg per step. A visual scale was used for the erectile response from 0 to 5 as normal erection. Duration and side effects were noted every 20 minutes until the beginning of detumescence.

Midodrine is an alphamimetic drug whose peripheral effects present 20 to 30 minutes after administration. Piloerection first appears on the head and slowly reaches the upper limbs, the chest, the abdomen and finally the lower limbs. Patients are aware of these sympathetic cutaneous effects. Systemic side effects are usually moderate with high blood pressure and bradycardia. Nevertheless, in this study cardiovascular monitoring was done every 15 minutes after drug administration for 2 hours. Midodrine was not used when hypertension, a low cardiac rate, severe heart disease or impaired renal function were already known. No patient was on cardiovascular drugs or any drugs contraindicating midodrine.

Penile rigidity was assessed after 3 hours and prolonged erection was managed by cooling procedures using ice or ether, or with penile vibrator stimulation. Detumescence was commonly established within a few minutes. A 15 mg dose of midodrine was given 30 minutes after the failure of first line treatment. The results of this oral approach were assessed at 30 minutes, and 1, 3 and 6 hours. In cases of a partial response or nonresponse another 15 mg midodrine were given once.

Of 354 patients 14 had a long lasting erection after ICI and were treated with oral midodrine. At 6 months the penile residual response was assessed by pharmacologically induced erection. All patients provided written informed consent with guarantees of confidentiality. The principles of the Helsinki Declaration were followed.

Within group analysis was performed using the matched pair t test to assess differences between the means of SBP, DBP and the heart rate. Statistical significance was considered at $p < 0.05$ for all statistical comparisons.

RESULTS

From January 2004 to March 2008 we performed 1,070 ICIs for erectile dysfunction in a total of 354 spinal cord injured patients. In 14 patients (3.9% or 1.3% of ICIs) priapism or prolonged erection was induced by the ICI procedure.

Median patient age was 35 years (range 20 to 61). Time since injury was 72.9 months. Of the cases 12 were ASIA A (motor and sensitive complete lesion) and 2 were ASIA B (motor complete and sensitive incomplete lesion). In 6 patients the spinal cord injury level was above T6, including 2 with tetraplegia (table 1). All patients were on intermittent catheterization. They were active and sat in a wheelchair most of the day. The bulbocavernosus and anal reflexes were missing in the 8 patients presenting with LMN lesions, while in 6 strong reflex activity was present at these areas. PGE1 was used with papaverine in 5 cases. All patients in the UMN group had a history of mild to moderate autonomic dysreflexia after visceral stimulation with penile vibratory stimulation or bladder distention. Three hours after ICI priapism was recorded in 14 patients, of whom none returned to the flaccid state after cooling procedures and penile vibromassage. Autonomic dysreflexia with high blood pressure and bradycardia occurred during prolonged erection in 2 tetraplegic cases. These cardiovascular symptoms spontaneously subsided before midodrine was given.

In 2004 at the beginning of our trial cavernous aspiration and irrigation were done in 2 patients without success. They then received oral treatment to induce flaccidity. Penile blood parameters were in accordance with an ischemic mechanism but cavernous puncture was not efficient.

At 30 to 45 minutes after oral medication complete penile flaccidity was achieved in 13 of 14 patients, which remained 3 and 6 hours later. In patient 7 a second 15 mg dose of midodrine was required 1 hour after the first treatment to achieve a totally flaccid penis 30 minutes later. After oral intake of midodrine all patients remained seated. Midodrine administration was well tolerated in all patients, including the 2 with tetraplegia. There was a moderate but significant increase in SBP and DBP at 30, 60 and 120 minutes compared with baseline with a corresponding significant decrease in heart rate (tables 1 and 2). These cardiovascular signs were mainly seen in the UMN group. Neurological side effects included piloerection in all patients and in-