Intracavernosal injection therapy is an effective therapy for men with erectile dysfunction (ED) who can not take oral agents or for whom oral agents are not effective. Initial dosing and dosage titration is typically individualized for each man, but there are general guidelines that can be followed. In caring for men who are beginning therapy with intracavernosal penile injections, the health care clinician is faced with many choices about starting dosages and titration of medications.

Injections are given with a 1 ml syringe with 1/2 or 5/8-inch length, and a 27 to 30-gauge needle. The injection may be given anywhere from the base of the penis to two-thirds of the way down the penile shaft at the 10 o'clock and 2 o'clock locations on the upper side of the penis away from the urethra and the head of the penis (see Figure 1). Injections are rotated within that area and the side of the injection is alternated with each injection. Many factors must be considered when determining a starting dose and titrating medication for patients. The goal of this treatment is to create an erection sufficient for sexual relations, while minimizing side effects such as pain or priapism.

Algorithm Development

The algorithm (see Figure 2) for titrating common vasoactive injectable agents for ED was derived from a literature review and over 13 years of experience working with patients receiving intracavernosal injections provide the basis for the algorithm designed to provide guidance with the dosage and titration of the injection medications.

Penile Injectable Medications for ED

Injection therapy has been an efficacious treatment option for patients since it was introduced in 1983 (Brindley, 1986). Efficacy for this treatment option is as high as 87% to 93% (Linet & Ogring, 1996; Porst, Buvat, Meuleman, Michal, & Wagner, 1998).

Injection therapy can be given as a single agent (monotherapy) with prostaglandin E-1 or a multi-agent mixture such as a trimixture of phentolamine, papaverine, and prostaglandin E1; a quadmixture of phentolamine, papaverine, prostaglandin E1 and atropine; or a bimixture of phentolamine and papaverine. Prostaglandin E1 can be compounded generically or is also dispensed as injectable alprostadil either as Caverject Impulse® or Edex®. While the Caverject Impulse or Edex systems are the FDA-approved drugs, some clinicians may use other forms of alprostadil. For example, some Veteran’s Administration hospitals still use individual bottles of powder and teach the patient to reconstitute with bacteriostatic water for injection.

FDA-approved medications (Caverject Impulse, Edex) are utilized first, unless otherwise specified by the referring health care professional (although some clin-
ics may not follow this practice related to cost factors). FDA-approved medications (Edex, Caverject Impulse) are more likely to be approved for insurance reimbursement than off-label compounded agents.

Seyam, Mohamed, Akhras, and Rashwan (2005) described the reasons for switching from monotherapy with prostaglandin to combination therapy with multiple vasoactive agents as pain, a lack of efficacy, and cost. These are the same reasons that I and the physicians I work with would switch a patient from prostaglandin E1 treatment. The main reason for switching from prostaglandin E1 to bimix, trimix, or quadmix is pain. Pain is the most common side effect for both Edex (Schwarz Pharma, 2004) and Caverject Impulse (Pharmacia, 2002) for men with ED.

Patients in my clinic who were post radical prostatectomy frequently reported pain in the penis as the injected Edex or Caverject Impulse began to work (about 10 to 20 minutes after injection). This complaint of pain in these patients fits with the hypothesis that pain is caused by activation of pain receptors via the prostaglandin in the time frame following prostatectomy when surgical incisions are still vulnerable to activation of local pain receptors. Trimix has been associated with decreased incidence of pain than with alprostadil alone (Baniel et al., 2000). If pain occurs with prostaglandin E1/alprostadil, the patient can be switched to trimix, quadmix, or bimix to decrease that side effect. The triple synergistic action of the three agents in trimix, which include prostaglandin E1, provides an erection utilizing

**Figure 2. Intracavernosal Injections Algorithm**

<table>
<thead>
<tr>
<th>Starting Dose and Medication Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients unless otherwise specified by referring MD</td>
</tr>
<tr>
<td>Previous use of injections – reinstate previous dose</td>
</tr>
<tr>
<td>If specified by MD, can start with this medication</td>
</tr>
<tr>
<td>Trimix (prostaglandin 10 mcg, phentolamine 1 mg, papaverine 30 mg)</td>
</tr>
<tr>
<td>No history of ED; age &lt; 60 = 0.1-0.2 starting dose</td>
</tr>
<tr>
<td>History of ED; age ≥ 65 = 0.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Erection at ≥ 6/10 strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes – Same dose at home</td>
</tr>
<tr>
<td>No - Titrate dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes – Switch to bimix (phentolamine 1 mg &amp; papaverine 30 mg)</td>
</tr>
<tr>
<td>No – Stay with trimix</td>
</tr>
</tbody>
</table>

| Increase dose by increments of 5-10 mcg (if bimix or trimix, increase dose by 0.1-0.3/10-30 units) to a dose sufficient for sexual relations. |

**Dose titration:** If erection 0-4/10 and pain is not an issue, double initial dose at next try (if pain is an issue go up by increments of 2.5 mcg each trial); if erection 5-6/10 increase by 2.5 initially (if bimix or trimix, increase by 0.1 ml/10 units). These are general recommendations, but the dosage should be individualized according to each participant’s response to the medication and any complaints of pain.

Depending on how strong the erection is, increase by increments of 2.5 mcg-10 mcg (if bimix or trimix, increase by 0.1-0.3/10-30 units) each trial until erection sufficient for penetration is achieved to a maximum dose of 40 mcg with prostaglandin and 1 ml of super trimix (30-2-20). If monotherapy with prostaglandin is not successful, the patient can be switched to trimix, which may be more effective starting at 0.5 ml of trimix initial dose and increasing to the maximum dose of 1 ml of super trimix. If this is still not effective, the patient could be switched to a quadmix adding atropine 0.15 mg/ml.

RP = Radical Prostatectomy
much lower doses of the prostaglandin. Baniel et al. (2000) described the incidence of pain with monotherapy of prostaglandin E1 as 48.5%, while incidence of pain with trimix was 2.9%, and 0 for quadmix and bimix. Pain increased with increased doses of prostaglandin. Bimix does not contain prostaglandin and therefore may be the ultimate choice for patients who complain of pain from the injected medications that contain prostaglandin. Patients for whom pain is a problem are switched to trimix, quadmix, or bimix in the algorithm.

Patients may also be switched to trimix or quadmix if the prostaglandin E1 injection is not effective. The synergistic effects of combination therapy with trimix and quadmix are typically utilized when monotherapy is not effective (Baniel et al., 2000; Kuan & Brock, 2001; Seyam et al., 2005). The trimix may be increased to a super trimix combination of the same papaverine 30 mg, while doubling both the phentolamine (to 2 mg) and the prostaglandin E1 (to 20 mg) in doses up to 1 ml maximum. Finally, if a single-agent prostaglandin and trimix are ineffective, atropine 0.15 mg/ml can be added to the trimix combination to create a quad mixture (Baniel et al., 2000; Montorsi et al., 2002).

The final reason for a change from Edex or Caverject Impulse to either generic prostaglandin E1 or multiagent therapy is cost. Edex and Caverject cost an average of

<table>
<thead>
<tr>
<th>Injectable Agent</th>
<th>Cost</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edex 20 mcg</td>
<td>$33-$38 per injection</td>
<td>Drugstore.com; Walgreens</td>
</tr>
<tr>
<td>Caverject Impulse 20 mcg</td>
<td>$33-$38 per injection</td>
<td>Drugstore.com; Walgreens</td>
</tr>
<tr>
<td>Prostaglandin E1 Compounded 20 mcg</td>
<td>$8-$10</td>
<td>Prescription Innovations of America; California Compounding</td>
</tr>
<tr>
<td>Trimix (prostaglandin E1 10 mcg, phentolamine 1 mg, papaverine 30 mg)</td>
<td>$2-$18 depending on dose</td>
<td>Prescription Innovations of America; California Compounding</td>
</tr>
<tr>
<td>Quadmix (prostaglandin E1 10 mcg, phentolamine 1 mg, papaverine 30 mg, atropine 0.15 mg)</td>
<td>$2-$20 depending on dose</td>
<td>Prescription Innovations of America; California Compounding</td>
</tr>
</tbody>
</table>

Table 2. Edex® Patient Cheat Sheet Handout

1. Wash hands with soap and water then dry. Open the medication cartridge packet.
2. Remove the paper seal from the base of the needle, being careful not to touch the needle.
3. Attach the needle to the tip of the Edex injection device.
4. Unscrew the blue portion of the plunger from the injection device.
5. Pick up the cartridge and wipe the colored tip of the cartridge with an alcohol swab.
6. Insert the cartridge into the injection device with the tip facing toward the attached needle. The groove on the injection device and the ridge on the cartridge need to be aligned for the cartridge to fit.
7. Reattach the blue plunger to injection device until tight.
8. Hold the injection in an upright position with the needle pointing up.
9. To prepare the drug solution; slowly push the plunger until the gray rubber stoppers touch. Then move the injection device in a back and forth motion until the solution is clear. Air bubbles may make it appear cloudy until they rise to the top after holding it upright again.
10. With needle facing the sky, remove the needle caps by pulling them straight off. Do not twist the caps. Do not touch the needle.
11. Gently tap the cartridge forcing the air bubbles to float to the top of the solution.
12. Push the plunger until the upper rim of the top stopper reaches the correct volume mark for the prescribed dose. Excess solution will be expelled from the needle.
13. Prepare the selected injection site as usual by wiping with an alcohol wipe.
14. To inject Edex, hold the injection device securely. Place the needle on the skin and then insert the needle completely. Place the thumb on the plunger and inject the solution.
15. Put the large needle cap on the needle and then unscrew carefully so you do not stick yourself with the needle. Discard the needle in container.
16. Remove cartridge and dispose in trash.
17. Clean the reusable injection device with warm water and mild soap before returning it to carrying case. DO NOT THROW AWAY! You will reuse this for future injections.

Source: Created by Jeffrey A. Albaugh, MS, APRN, CUCNS
Preparing and injecting the medication is done utilizing a prosthetic model of the penis. The final step of teaching is for the patient to return demonstrate appropriate technique for preparing and injecting the actual intracavernosal injection. Any questions are answered and the patient is evaluated for the strength of the erection and adverse side effects (especially pain). The patient is taught to rotate injection sites with each injection and how often he can safely use the injections (Edex and Caverject prescribing guidelines recommend no more than 3 times a week and once in 24 hours to prevent corporal scarring).

The patient is given contact information for the advanced practice nurse and told to report back on how the injection therapy went at home with the determined next doses of injections. Contact information is also obtained from the patient for followup purposes and it is essential to communicate with patients after they have initiated treatment at home. Often patients may have questions or concerns about the injections or dose titration and they always appreciate the follow-up communication to ensure they are progressing with the treatment appropriately. Some clinicians may prefer to do further titrating of medications in the clinic and additional instruction may be needed for patients when they switch to different agents.

The patient is instructed to return demonstrate appropriate technique for preparing and injecting the medication. Edex or Caverject Impulse, he watches the video instruction provided by the appropriate manufacturer. All patients are given both verbal and written instructions on how to prepare and self-inject the medication, side effects, and what to do if problems occur (including priapism, Peyronie’s disease, and pain). The client’s partner may need to be the one injecting the medication if the client is unable. Manufacturer’s written instructions are given to patients who use Edex or Caverject, while the written instructions I developed were created for use with generic prostaglandin or multi-agent compounded medication. Additional written instructions may be available through some of the compounding pharmacies such as the directions supplied by University Compounding Pharmacy (http://www.ucprx.com/ed_dysfunction.htm). I also developed a supplemental one-page patient education handout for each of the injectable agents to provide a quick, simple reference for patients (see Table 2).

After the patient receives written and verbal instructions, a demonstration of the technique for preparing and injecting the medication is done utilizing a prosthetic model of the penis. The final step of teaching is for the patient to return demonstrate appropriate technique for preparing and injecting the actual intracavernosal injection. Any questions are answered and the patient is evaluated for the strength of the erection and adverse side effects (especially pain). The patient is taught to rotate injection sites with each injection and how often he can safely use the injections (Edex and Caverject prescribing guidelines recommend no more than 3 times a week and once in 24 hours to prevent corporal scarring).

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Utilization of intracavernosal injections by investigators reveals varied initial dosing and titration regimens. In one study, titration with alprostadil (prostaglandin E1) was started at the 5 mcg dose and increased by intervals of 5 mcg with most of the men responding to the 2.5 to 15 mcg range (Brock, Tu, & Linet, 2001). Montorsi et al. (2002) also began with an initial dose of 5 mcgs and titrated to an effective dose of prostaglandin. Another investigator used a 5 mcg starting dose initially and switched to 10 mcgs in subsequent studies as a starting dose with titration of medication up to 40 mcg (Goldstein et al., 2000). Richter et al. (2001) used a starting dose of 5 mcg with all patients,
titrating up by 5 mcg to achieve an erection sufficient for sexual relations with a maximum dose of 30 mcg.

Typically trimix (papaverine 30 mg, phentolamine 1 mg, and prostaglandin E1 10 mcg) and bimix (papaverine 30 mg and phentolamine 1 mg) are started at a dose of 0.1 to 0.5 ml in my clinical practice depending on the patient’s age and concomitant problems for ED. Investigators have utilized dose volumes of trimix (papaverine 30 mg, phentolamine 1 mg, and prostaglandin E1 10 mcg per 1 ml) ranging from 0.18 to 1.0 ml in previous studies (Bennett, Carpenter, & Barada, 1991; Montorsi et al., 2002; Mulhall et al., 1999). One physician, who only sends post prostatectomy patients for referral, prefers only trimix with post radical prostatectomy patients related to the side effect of pain with monotherapy using prostaglandin E1. For this reason, this physician’s patients are immediately started on dose titration of trimix, foregoing the monotherapy with prostaglandin E1/alprostadil.

**Summary**

Although each man’s individual circumstance and history must be carefully considered and titration individualized accordingly, general guidelines can be used to determine initial dosing and medication titration for intracavernosal injection treatment. In my clinical practice, this algorithm has been utilized as a general guide for initial dosing and titration of commonly used vasoactive intracavernosal injectables. It is essential that health care professionals continue to provide comprehensive one-on-one teaching and followup for patients and their partners who will be using intracavernosal injection therapy for erectile dysfunction. Comprehensive education on this treatment option can decrease the chance of adverse events (for example, teaching the patient to rotate injection sites to avoid scarring leading to Peyronie’s disease or applying pressure at the injection site for 5 minutes immediately after injection to prevent bleeding) and can assist the patient to find the correct dose and medication to bring about an erection sufficient for sexual relations. With the help of a trained professional, patients can successfully learn to incorporate intracavernosal injection therapy into love play with their partner.

**References**


