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Comparative Tolerability and Efficacy of Treatments for Impotence

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Abstract

Modern pharmacological treatment of impotence is determined by the presenting symptoms. Since this involves symptomatology with a heterogenous aetiology, many different drugs are involved in the treatment of impotence.

Drugs used for libido and arousal problems include testosterone, yohimbine, trazodone and apomorphine. Since patient self-assessment is the only parameter that can be used to measure the result of treatment and positive results are seldom affirmed, no positive benefit of these agents can be assumed at present.

Oral medications for erectile dysfunction include yohimbine, trazodone, apomorphine, phentolamine, arginine and sildenafil. Of these drugs, sildenafil has been the most systematically studied for effectiveness, but long term safety data await the results of post-marketing surveillance.

Of the ejaculation disorder therapies, treatments for premature ejaculation are the best studied. Favourable results have been obtained with clomipramine, paroxetine and fluoxetine. The safety of these medications has been assessed through their long term use in psychiatry.

Intracavernous self-injections for erectile disorders are performed using a variety of drugs and drug mixtures. Only alprostadil and the combination of papaverine with phentolamine are widely used. Alprostadil is very well tolerated; however, penile pain is a serious problem in a significant proportion of patients. Papaverine in combination with phentolamine is effective, but penile fibrosis and priapism occur more often than with the use of alprostadil. Several new developments in this area are currently under way.

Alternative routes for medication for erectile dysfunction include ointments and patches to the penile skin and the glans. Only transurethral alprostadil, 'MUSE' (medicated urethral system for erection) has been shown to be effective in large trials. Long term safety still has to be demonstrated, but the 1-year safety profile is encouraging.

In general, the end points of impotence treatment studies are very diverse so efficacy data can only be assessed in comparative studies. However, long term comparison studies have not been performed. Safety demands must be set very high for this type of treatment since the disorders being treated present no threat to the patient's health.

Sexual dysfunction in men can be treated in several ways. Different approaches, e.g. consultation with a sexologist, medical treatment and surgery for erectile dysfunction may have to be combined for optimal results. However, a risk-benefit assessment of psychotherapy, mechanical devices, vascular surgery and of the implantation of a penile prosthesis are beyond the scope of this review.

Male sexual dysfunction is a term for a heterogenous group of symptoms. Low libido, arousal difficulties, erectile dysfunction, ejaculation disturbances and anorgasmia need to be distinguished from each other. It may be helpful for reasons of patient counselling and for treatment selection to have an hypothesis about the main cause of the dysfunction, an estimation of the severity of psychosexual problems that may play a concomitant role, and an accurate assessment of physical abnormalities that contribute to the symptoms. The aetiology of the dysfunction is relevant for risk-benefit assessments.[1] For example, penile fibrosis might be an acceptable risk in a 70-year-old patient with erectile dysfunction following a prostatectomy for carcinoma; however, for a young, otherwise healthy, patient with an arousal problem, fibrosis as a result of treatment would be totally unacceptable.

When male sexual dysfunction does not respond to counselling by a sexologist, pharmacotherapy is the next option. Oral medication is the first treatment modality to consider. Overall success of medical treatment is related to the residual function available; for example, is there still intimacy between partners, is the patient still sexually active in spite of his erectile dysfunction and are sleep-erections still present? The more physical abnormalities play a role in the aetiology of the dysfunction, the less likely that medical treatment will be helpful. Intracavernous injection therapy is the most effective treatment option for patients with erectile failure, patients with cardiovascular comorbidity needing higher doses.

In this paper we discuss the following medical treatment options: oral medication for libido and arousal problems; oral medication for erectile dysfunction; oral medication for ejaculation disorders; intracavernous injection therapy; and alternative routes for medication.

1. Physiology of Erectile Function

An extensive review on the physiology of penile erection has been published by Andersson and Wagner.[2] It can be summarised as follows. The initiation of an erection is a neurogenic event. The impulses may originate from the brain (as is the case in rapid eye movement sleep erections) or may derive from sacral reflexes (as can be observed in some patients who are paraplegic). In normal circumstances, a combination of both will serve as an initiator.

Dilation of the arteria cavernosa and the helicine arteries is controlled by well known neural regulation mechanisms. These are, however, not sufficient for the development of a rigid erection, owing to shortcuts to the venous channels and because the resistance of the lacunar spaces in the corpora cavernosa depends on smooth muscle tone. Relaxation of the smooth muscles is necessary for the expansion of the corpora, which is initiated by parasympathetic impulses. Sympathetic tone, contracting the smooth muscle cells, needs to be reduced.

After the first impulses, the scarcely innervated network of endothelial cells and smooth muscle cells take care of their own coordination in order to relax all at the same time. Nitric oxide (NO) is attributed a crucial role in these events.[3,4] Free inflow of blood is allowed in the lacunae, finally resulting in such a tumescence that outflow of blood will be stopped by compression of the venous channels between the distended corporal tissue and the tunica albuginea. This leads to rigidity of the penis that may be further enhanced by contractions of pelvic floor muscles, compressing the crurae of the corpora cavernosa and building a pressure that is higher than the systolic blood pressure.[5] Inflow of blood to the corpora cavernosa is minimal at this point.

The erection comes to an end by renewed contraction of the smooth muscle cells, initiated by sympathetic impulses and by the production of substances such as endothelin-1, prostaglandin $F_{2\alpha}$ and thromboxane A_2 by the endothelial cells.[2,6] This allows venous outflow by decompression of the subtunical venous plexus.

Over the past 20 years, the fundamental role of the vascular endothelium has been established in cardiovascular function, as has been recently summarised by Ferro and Webb.[7] Endothelial cells produce both vasodilating substances among which prostacyclin and NO, as well as vasoconstricting substances. NO is synthesised from arginine by a number of NO synthases. The isoform normally expressed in endothelial cells is calcium-dependent and may be activated by several stimuli including shear stress, hormones and receptor-mediated agonists, e.g. acetylcholine and bradykinin. NO exerts its effects in the vascular smooth cells to which it diffuses, by increasing intracellular cyclic guanosine monophosphate (cGMP) levels which, in turn, lower intracellular calcium levels. Termination of cGMP action occurs through breakdown of cGMP by phosphodiesterase type V in the corpus cavernosum.

NO has been described as the propagator of a series of events resulting in relaxation of all smooth muscle cells of the corpora.[3,4,8,9]

Prostacyclin is another endothelium-dependent vasodilator.[7] It is assumed that the vasodilating prostaglandin alprostadil (prostaglandin E_1) acts via the same receptor as prostacyclin, generating cyclic adenosine monophosphate (cAMP), which gives rise, in the same way cGMP does, to smooth muscle relaxation.

2. Pharmacological Aspects of Erection Disorder Therapies

Since the corpora cavernosa may be regarded as blood vessels (or blood derivatives),[10] it is obvious that pharmacological influences may come from the sympathetic nervous system (where stim-

ulation is anti-erectile), the parasympathetic nervous system (which is necessary for triggering NO release) as well as from prostaglandins and prostacyclins.

The following substances are in use or have been use as erectants:

- sympatholytics: yohimbine, phentolamine, phenoxybenzamine, moxisylyte
- prostaglandins: alprostadil
- muscle relaxants: papaverine
- miscellaneous agents: serotonergic drugs (e.g. trazodone), dopaminergic drugs (e.g. apomorphine), NO donators or effect-enhancers (e.g. nitroglycerin, linsidomine, sildenafil).

Combinations of these substances are often used.

However, many of these substances are only used occasionally and, with a few exceptions, systematic (clinical) pharmacological investigations have not been performed.

2.1 Yohimbine

Yohimbine is an α_2-adrenoceptor blocker with a short duration of action. It has been given orally for the treatment of male impotence and for its alleged aphrodisiac properties. Blockade of α_2-adrenoceptors with selective antagonists such as yohimbine can increase sympathetic outflow and potentiate the release of norepinephrine (noradrenaline) from nerve endings, leading to an activation of α_1- and β_1-receptors in the heart and peripheral vasculature with a consequent vasoconstriction.[11] Currently, it is assumed that yohimbine exerts its erectogenic effect through a central action.[12]

2.2 Phentolamine

Phentolamine is a nonselective α-adrenoceptor blocking agent. Although like yohimbine, nonselective α-adrenoceptor blocking agents may also provoke a reflex, increasing sympathetic outflow and release of norepinephrine, they also inhibit vasoconstriction.

2.3 Moxisylyte

Moxisylyte, also known as thymoxamine, is an α-adrenoceptor blocking agent that competes with norepinephrine at receptor sites. It has been studied in humans.[13] In addition, its pharmacokinetics after intravenous and after intracavernous injection therapy have been studied in healthy volunteers.[14,15] In these studies, the pharmacokinetics of moxisylyte have been largely elucidated. Although the parent compound is rapidly degraded after injection by nonspecific esterases, the metabolites desacetylmoxisylyte and monodesmethyl desacetylmoxisylyte are also pharmacologically active and, in the case of the intracavernous injection, systemic spread is rather fast. At least for this drug, intracavernous injection therapy can not be regarded as purely local administration.

2.4 Alprostadil

In 1985, Hedlund and Andersen[16] reported the effects of prostanoids on human penile tissue and since then alprostadil has been a frequently prescribed drug for the treatment of erectile dysfunction. Alprostadil binds with the prostaglandin E receptors and the relaxing response is mediated by the cAMP system.

2.5 Papaverine

Papaverine is a smooth muscle relaxant and a vasodilator. The main pharmacological action of this agent is a nonspecific vasodilatory effect on the smooth muscle of the arterioles and capillaries of all vascular beds. This action has been related to phosphodiesterase inhibition. Various vascular beds and smooth muscle respond differently in intensity of action and duration. The haemodynamics of papaverine and phentolamine-induced penile erection following intracavernous injection have been investigated.[17] It was concluded that papaverine decreases the resistance to arterial inflow and increases the resistance to venous outflow.

Although papaverine-phentolamine preparations are being used for pharmacological self-injection programmes, their chemical properties following

administration to patients have not been described adequately in the literature. The pH of papaverine-phentolamine solution is <4 and a precipitate occurs at a pH >5. The effect of an acidic solution on corporal connective tissue and smooth muscle meshwork is unknown, but precipitation of papaverine-phentolamine at pH >5 may cause primary intracorporal scarring.[18]

2.6 Nitric Oxide

NO appears to be involved in neurotransmission processes that lead to smooth muscle relaxation in the corpus cavernosum permitting penile erection.[3,4,8,9] Pharmacotherapeutically, NO has to be derived from NO donors such as organic nitrates, or from its precursor, arginine, by the action of NO synthase. The NO donor linsidomine has been used in humans.[19]

2.7 Sildenafil

Sildenafil is a selective inhibitor of cGMP specific phosphodiesterase type V and it inhibits the degradation of cGMP. In the corpora cavernosa, the predominant type of phosphodiesterase is type V. Thus, it is supposed that selective inhibition of phosphodiesterase type V will facilitate the NO driven relaxation of smooth muscle of the corpus cavernosum.[20] Phosphodiesterase type V is also present in platelets, rods and cones of the eye, and in the lung.[21]

2.8 Trazodone

Trazodone is an antidepressant, which has been attributed with significant actions at serotonin (5-hydroxytryptamine; 5-HT) receptors and which is known for its libido-improving properties[22,23] and also for causing priapism as a adverse effect.[24,25] It has been advocated as a penile erectant drug, but in a double-blind trial Meinhardt et al.[24] could not demonstrate the efficacy of oral trazodone 150 mg/day versus placebo. Trazodone has also been used intracavernously. It is not known whether the parent substance trazodone or a metabolite, e.g. m-cpp, is responsible for the effects seen.

3. Pharmacotherapy

3.1 Oral Medication for Libido and Arousal Problems

Dopaminergic, serotonergic and adrenergic systems in the brain are important for sexual desire.[27,28] Many neurotransmitters and neuropeptides play a role in sexual behaviour.[2,28] For stimulation of the dopaminergic and the serotonergic pathways testosterone needs to be present.[29,30] When low libido is related to low serum testosterone, a trial period with testosterone supplementation is indicated. For reliable testosterone serum levels this is best done with injectable depot preparations. If this approach is successful, and continuation is desired, the physician may want to switch the patient to oral testosterone, but first pass liver toxicity and unreliable serum levels make this option less attractive.

Of the oral preparations, the long term safety of testosterone undecanoate has been demonstrated in >10 years of use.[31] A testosterone patch placed on the skin may be the route of choice for many patients. However, skin irritation and dislodgement of the patch are the major drawbacks of this system. Trazodone is known for its libido-improving properties.[22,23] The positive effect of yohimbine on libido has been referred to in the literature, but has not been studied systematically in humans. A positive effect on sexual motivation was shown in the rat model; however, enhancement of sexual arousal could not been demonstrated in healthy human volunteers.[32,33]

Apomorphine, a dopamine agonist, has a positive effect on sexual arousal in the rat model.[34] In humans this effect could not be confirmed in healthy volunteers.[32] Presently, it is not customary to distinguish sexual arousal problems from low libido as a separate indication for medical treatment and the term 'prosexual agent' is used for both libido and arousal problems.[28,30]

3.2 Oral Medication for Erectile Dysfunction

In the 1980s, yohimbine was studied as a treatment for erectile dysfunction in placebo-controlled trials with reasonable efficacy and no significant adverse effects.[35-38] Recently, however, it was found to be ineffective in a group of patients with erectile dysfunction of mixed aetiology.[39] Ernst and Pittler[40] conducted a meta-analysis and concluded however, that the benefit seems to outweigh the risks. Therefore, on the basis of this meta-analysis, they suggest that yohimbine is a reasonable therapeutic option for erectile dysfunction.

The adverse effects of yohimbine in clinical trials were not serious, but the drug is probably contraindicated in patients with cardiovascular problems. Ernst and Pittler[40] mention publication bias for positive results as one of the possibilities for their unexpected results (i.e that the benefit seems to outweigh the risks of yohimbine).

The conclusion regarding yohimbine of Ernst and Pittler,[40] following their meta-analysis of the literature is different of the conclusion of the American Urologic Association (AUA) panel.[41] However, this may be explained by the fact that more recent trials were included in the meta-analysis by Ernst and Pittler.[40] Therefore, it can be seen that results are not consistent and recent literature recommends that yohimbine is considered only for patients with psychogenic impotence and that it is given in combination with trazodone to enhance effectiveness.[42]

Trazodone is used for oral treatment of erectile dysfunction since, in addition to its serotonergic effects on the brain, it has peripheral α-blocking properties and so prolongs erections.[25] However, in a double-blind trial, trazodone could not be shown to have a better effect than placebo.[26] Its adverse effects, such as drowsiness, sleepiness and nausea do not make it an attractive treatment option. The α-blocking properties of drugs may be helpful, but are by themselves insufficient for the initiation of an erection.[2] Likewise, oral phentolamine was found helpful in the treatment of erectile disorders.[43]

Oral (buccal) apomorphine has been used to induce erections in patients with psychogenic impotence.[44] With the buccal route of administration absorption, adverse effects, such as nausea and vomiting, were believed to be milder. However, these results await confirmation.

Sildenafil, a phosphodiesterase inhibitor, has been proven to be an effective treatment in patients with impotence of a psychogenic aetiology.[45] It has also been shown to be effective in patients with erectile dysfunction due to diabetes.[46] In patients with spinal cord injuries reflex erections improved in quality following treatment with sildenafil.[47]

Up to 1-year use of sildenafil has been studied in more that 2000 patients. The main reported adverse effects were headache (16%), flushing (10%), gastrointestinal complaints (7%) and nasal congestion.[48] The adverse effects in the study of Lue et al.[49] were dose-related. Disturbance of colour vision with high doses (100mg or more) is possible. The use of nitrates is an absolute contraindication for the use of sildenafil. The adverse effect profile of sildenafil will only be known when the drug is used in larger patient groups for longer periods of time and may be related to the presence of phosphodiesterase type V in other tissues other than the corpus cavernosum (e.g. platelets, rods and cones and the lung), or to the effects of sildenafil on phosphodiesterase type VI. Acute myocardial infarction associated with sildenafil use has been reported.[50]

The NO precursor arginine has been tested in humans; however, the preliminary favourable data have not been confirmed.[51]

In several trials clinical trials of treatments for erectile dysfunction, patients receiving placebo have been seen to show an improvement; success rates with placebo of up to 40% have been reported. This placebo effect may explain why the use of many drugs has been advocated. Some agents have been studied again following positive trial results and have not been shown to be any more effective than placebo. For example, in later, placebo-controlled trials, pentoxifylline was found to be ineffective in patients with diabetes mellitus[52] and in patients with vascular erectile disorders,[53]

isoxsuprine proved to be ineffective in patients with vascular problems[53] and clomiphene did not help erectile dysfunction in patients with secondary hypogonadism.[54]

3.3 Oral Medication for Ejaculation Disorders

Ejaculation is an event controlled by the sympathetic nervous system. In the CNS serotonergic control is important in the control of ejaculation.[27]

Retrograde ejaculation is treated with success in one-third of the cases with ephedrine sulfate 50mg or with imipramine 75mg.[55] The use of pseudoephedrine and phenylpropanolamine has also been advocated.[56] For retarded ejaculation, use of cyproheptadine has been advocated.[57] The use of cyproheptadine has been reported to counteract ejaculation disturbances due to antidepressant medication; but since it causes fatigue and may induce a relapse of the depression it is not recommended in this setting.[27]

The treatment of premature ejaculation has been evaluated with clomipramine,[58,59] paroxetine,[60] fluoxetine,[61,62] and sertraline.[63] Placebo was less effective than these medications. Clomipramine 25mg, taken 12 hours before intercourse, prolonged ejaculation latency time. However, clomipramine was not effective in men with concomitant erectile dysfunction.[59] Treatment with fluoxetine 20 to 40 mg/day may improve the intravaginal ejaculation latency time from 30 seconds to 3 minutes.[62] Paroxetine 20 mg/day may improve the intravaginal ejaculation latency time from an average of 13 seconds to 300 seconds.[64]

The adverse effects of these medications are known from their use in psychiatric indications and these include nausea, headache and insomnia. In a comparative study of treatments for premature ejaculation, clomipramine was more efficacious then the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) sertraline and fluoxetine; however, it caused more adverse effects.[65]

3.4 Intracavernous Injection Therapy for Erectile Dysfunction

Alprostadil is given as an intracavernous injection on its own or in combination with other agents, for example, papaverine and/or phentolamine.[66-69] The efficacy of alprostadil and the incidence of adverse effects have been found to be dose-dependent.[70] Adequate doses are considered to be doses of 5 to 20μg. No clinical differences between the various formulations of intracavernous alprostadil have been found.[71] Worldwide experiences with alprostadil in erectile dysfunction have been described by Porst.[72] He concludes that for self-injection therapy, alprostadil currently represents the most efficacious and safest pharmacological option. Recently, the treatment of erectile dysfunction in men with transurethral alprostadil, 'MUSE' (Medicated Urethral System for Erection) has been described and is discussed in section 3.5.[73]

Intracavernous phentolamine is most often used in combination with another agent, e.g. papaverine or alprostadil. Self-injection of small doses of phentolamine (usually 0.5 to 1mg) combined with papaverine (usually 2.5 to 37.5mg, and most commonly 30mg), or with alprostadil 5 to 10μg into the corpus cavernosum is effective in the treatment of impotence.[17,66,74,75]

In a literature review conducted in 1989, Jüneman and Alken[76] gave figures for effectiveness and adverse effects of papaverine monotherapy and of papaverine combined with phentolamine and of alprostadil.[76] Papaverine as monotherapy, at a dose of 80mg, is less effective and causes priapism and penile fibrosis more often than papaverine 30mg combined with phentolamine 1mg. In a double-blind, crossover trial, intracavernous injection therapy with papaverine 40mg and papaverine 20mg plus phentolamine 0.5mg were compared. The combination preparation was significantly better than papaverine alone.[77] Thus, the combination is to be preferred above papaverine as monotherapy.

Alprostadil causes priapism and fibrosis less often than papaverine. However, penile pain is in-

duced more frequently than with the use of papaverine plus phentolamine. More recently, Porst[78] concluded the following about the problem of comparing the incidence of penile fibrosis with different treatments: 'Therefore from the scientific point of view, no comparisons between the different drugs are possible with reference to local fibrotic side-effects.' On the basis of the results of 2 large pharmaceutical company sponsored trials, local fibrotic changes in the penile tissue would be expected to occur in 5 to 10% of patients following intracavernous use of alprostadil for more than 2 to 3 years.[78,79] Porst[78] estimates that the combination of papaverine plus phentolamine causes local fibrotic changes 2 to 3 times more frequently.[78]

In a recent study, pain was reported by 50% of the patients using alprostadil; however, the only occurred after 11% of injections.[80] Only 6% of patients experienced so much pain that they stopped the use of alprostadil. The mechanism by which the pain is caused by alprostadil is not well understood. It is unlikely to be the result of the acidity of the injection fluid; alprostadil-containing preparations are less acid than papaverine-containing solutions.[81] In our own experience, an alprostadil-containing solution with a pH of 5.8 to 6.2, but without any buffer capacity, pain still was a problem in a relevant amount of patients.[82] Alkalisation with sodium bicarbonate does not alleviate pain, although this has been propagated,[83,84] but adding a local anaesthetic to the injection fluid may be helpful.[85,86] The speed of the intracavernous injection therapy is relevant, slower injections (60 seconds) causing less pain than fast injections (5 seconds).[87]

Alprostadil has been shown *in vitro* to suppress collagen synthesis,[88] but the relevance of this phenomenon is speculative in clinical practice.

In general, the haemodynamic response of the cavernosal arteries to intracavernous injection therapy improves after long term use; this effect has been shown for alprostadil as well as for the combination of papaverine and phentolamine with alprostadil.[89] Data collected in a patient group, in which intracavernosal therapy with various agents was started more than 5 years previously, showed that long term complications were relatively minor.[90] However, this seems in contradiction with the finding that the incidence of fibrotic nodules doubles every 3 months of follow-up and may be found in 30% of patients after 1 year of treatment with papaverine-containing solutions.[91,92]

In a review on practical therapeutics, Bénard and Lue[93] judged that the self-administration of intracavernous injection therapy is well tolerated, minimally invasive and highly effective, provided that the proper technique is used. However, comparative studies have only been performed on the efficacy of different intracavernous injection therapies in test situations and not in long term home use.[94-96] Comparison of different drugs for intracavernous injection therapy is further complicated by differences between methods applied and preparations used,[97] efficacy differences due to injection technique (slow versus quick and with or without tourniquet) and due to differences in concentration and volume applied. In fact, the choice between alprostadil and the papaverine plus phentolamine combination is made in clinical practice on the base of commercial availability and cost/reimbursement policies of insurance companies.

Alprostadil is registered in the US and many other countries, the combination of papaverine with phentolamine is registered in some European countries.

Improvements in safety and effectiveness has been sought in 2 ways: by combining alprostadil, papaverine and phentolamine at reduced doses; and by the use of new drugs for intracavernous injection therapy. The combination of papaverine with phentolamine and with alprostadil is effective.[98] This effectiveness seems to be enhanced by adding atropine.[99] Virag and colleagues, advocate a mixture of 6 drugs.[100] However, the combinations with papaverine still have the problem of causing fibrosis in some patients, even if only papaverine 4.5mg is used.[82,101] Combinations with alprostadil may cause penile pain, depending on the dose of alprostadil used: it is very rare when the dose is only 1.5μg.[82] In clinical practice, a registered

drug is preferred, since the advantages of combinations are only marginal.[10]

Vasoactive intestinal peptide, calcitonin-related peptide, linsidomine and forskolin have been used in intracavernous injection programmes.[19,102-104] In some cases it was possible to induce erections in patients whose condition did not respond to the more conventional drugs. However, availability, cost and the only marginal advantages compared to the drugs already available has delayed their introduction into clinical use. Currently, the combination of vasoactive intestinal peptide with phentolamine has been submitted for approval in several countries. The α-blocker, moxisylyte, facilitates erections in sexual stimulating circumstances. Because it is expected to be a very well tolerated drug, it will soon become commercially available for intracavernous use. However, moxisylyte is less effective than alprostadil.[105] The long term safety of intracavernous injection of linsidomine in monkeys has been described by Van Heyden et al.[106] The authors conclude that linsidomine would appear a well tolerated option for intracavernous pharmacotherapy of erectile dysfunction.

3.5 Alternative Routes

Drugs applied on the penile skin, on the glans penis or in the urethra may have an erectogenic effect. Since the corpus spongiosum does not have a tunica albuginea medication may reach it more readily than the corpora cavernosa. Vascular communications exist between the corpus spongiosum and the corpora cavernosa.[107] A constricting band on the base of the penis makes transurethrally applied medication more effective, so it is likely that the drug reaches the corpora cavernosa through localised spreading and not via the general circulation.[108] Vascular channels between the corpus spongiosum and the corpora cavernosa may simply provide a channel for drug transport, but may also conduct the impulses for smooth muscle relaxation by their endothelial and smooth muscle cell connections.

Transcutaneous application of papaverine, nitroglycerin (glyceryl trinitrate) and minidoxil have been tested with positive effects in selected patients.[109-111] The integrity of the cavernous physiology is a prerequisite. Transcutaneous medication has been useful in some of the patients with psychogenic erectile dysfunction and may be a good alternative for patients with a neurological cause of erectile dysfunction, who are very sensitive to intracavernously applied drugs and in whom priapism occurs even after the application of a very low intracavernous dose.

'MUSE' has been shown to be an effective method to induce an erection. A little pellet containing alprostadil is applied in the meatus urethra with the aid of an applicator. The alprostadil dose used to induce an erection is 50 times higher by this route as it is for the intracavernous route because not all the alprostadil reaches the corpora cavernosa.[112] With home use, half of the 65 patients in a double-blind study achieved erections rigid enough for intercourse. Tenderness is the most important adverse effect with 'MUSE', the frequency of occurrence is dose-dependent; 9.1 to 18.3% of patients experience tenderness using alprostadil doses of 125 to 1000μg.[112]

In a study of 103 patients with erectile dysfunction, alprostadil delivered by the 'MUSE' system, at a dose of up to 1000μg, was compared to alprostadil given by intracavernous injection therapy at a dose of up to 20μg.[113] The response rate with 'MUSE' was 43% versus 70% with the intracavernous injection therapy. 'MUSE' was associated with urethral bleeding in 4.8% of the patients; this adverse effect was not seen with intracavernous injection therapy. 'MUSE' was associated with dizziness, sweating or hypotension in 5.8% of patients; no patients receiving intracavernous injection experienced these symptoms. Penile pain or burning was reported by 31% of the 'MUSE' users and by 10.6% of the intracavernous injection alprostadil users. Porst[113] concludes that 'MUSE' should be reserved for a subset of patients suffering from erectile dysfunction.[113]

4. Specific Conclusions

4.1 Oral Medication for Libido and Arousal Problems

Several drugs are available that are likely to have an influence on libido or on arousal. Since no validated method is available for quantification of these problems, the efficacy of medical treatment cannot be reliably evaluated yet.

4.2 Oral Medication for Erectile Dysfunction

The AUA Erectile Dysfunction Clinical Guidelines Panel concludes in its report on organic erectile dysfunction that the efficacy of oral drug therapy with yohimbine clearly remains to be proven, while they consider the status of oral phentolamine, trazodone and pentoxifylline investigational.[41] In this report the AUA panel searched the literature up to January 1995. Since this time, the efficacy of sildenafil has been demonstrated and 1-year safety data are favourable.

Because erectile dysfunction is a multicausal problem and the patient group is heterogenous, it is most unlikely that one cure will be appropriate to all. Obviously, a young patient with performance anxiety needs a different treatment than the older patient who is taking cardiovascular drugs. Trials should concentrate on well defined subgroups of patients, with clearly stated end-points for efficacy.

4.3 Oral Medication for Ejaculation Disorders

The efficacy of several SSRIs has been proven for treatment of premature ejaculation. A comparison between clomipramine and several SSRIs showed greater effectiveness, but more adverse effects with clomipramine. The next step should be a comparison between daily medication and taking the drug on demand. The efficacy of several sympathicomimetics has been shown in retrograde ejaculation; however, comparative studies have not been reported. For retarded ejaculation treatment the literature is anecdotal.

4.4 Intracavernous Injection Therapy

Intracavernous injection therapy is the most effective pharmacological treatment for erectile dysfunction. However, the treatment discontinuation rate for intracavernous injection therapy programmes is 50% in many studies. The reasons for discontinuing are, for the majority, not treatment-related problems, but involve factors such as recovery of erectile function, loss of partner, deterioration of health, etc.[114] This is one of the main reasons why comparative long term studies have not been performed and are not likely to be performed in the near future. However, much data are available about long term use, and it is clear that long term use of alprostadil, and of the combination of papaverine with phentolamine, is well tolerated. The major drawback of intracavernous injection therapy is the possibility of fibrosis of the corpora cavernosa. With the use of alprostadil this is less likely to occur than with the combination of papaverine with phentolamine.

4.5 Alternative Routes for Medication

The reports of efficacy with medication used transcutaneously have not been confirmed in large series and this route of administration is likely only to benefit patients who are oversensitive to intracavernous drugs.

Only the 'MUSE' system with alprostadil has been studied in large numbers of patients and this system seems to be effective and well tolerated, although long term follow-up is not available yet. One-year use showed acceptable safety. In comparison with alprostadil intracavernous injection therapy, 'MUSE' it is less effective.

5. Overall Conclusions

A risk-benefit assessment could be performed using the merit assessment model as described by Edwards et al.[1] In this system 'seriousness of diseases' is a part of the grading system. Taking this into consideration, any serious adverse effect caused by a therapy for impotence would be deemed unacceptable. Measuring the improvement

produced by the drug is of crucial importance. For treatment of erectile dysfunction, this is highly dependent on the amount of disability present at the start of therapy. There is no accepted quantitative measure to score this. The several oral treatment options, such as oral phentolamine, yohimbine combined with trazodone, buccal apomorphine and sildenafil, need to be compared for effectiveness. Presently, any oral treatment is less effective than intracavernous injection therapy.

Intracavernous injection therapy treatment with alprostadil or with the combination of papaverine and phentolamine has been well studied. Both treatments are effective, but alprostadil is associated with less adverse effects.

For treatment of preterm ejaculation, time to ejaculation after vaginal penetration is a rational end-point and it is used in some studies. Several SSRIs and clomipramine may be useful in the treatment of this condition.

For treatment of libido and arousal problems, the only measure available is self-assessment by the patient and this makes this a difficult area to study.

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