Efficacy and Safety of Intracavernosal Alprostadil in Diabetic Patients with Erectile Dysfunction

by

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Dedicated to

My late father, Lalitchandra

My mum, Vilas

My wife, Rupal

My son, Arin

My daughter, Anjali

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ABBREVIATIONS

AE	Adverse Event
AEF	Adverse Event Form
AGE	Advanced Glycosylation End Products
AMP	Adenosine Monophosphate
ATP	Adenosine Triphosphate
CRF	Case Report Forms
DM	Diabetes Mellitus
ED	Erectile Dysfunction
GMP	Guanosine Monophosphate
IIEF	International Index of Erectile Function
MMAS	Massachusetts Male Ageing Study
NIH	National Institute of Health
PGE_1	Prostaglandin E_1

Abstrak

Pengenalan

Ramai pesakit kencing manis mengalami masalah kegagalan ereksi. Alprostadil atau Prostaglandin E1, pernah digunakan untuk merawat kegagalan ereksi melalui cara intrakavernosa dan di dapati memberikan hasil yang memuaskan. Walau bagaimanapun, keputusan kajian menunjukkan pesakit kencing manis kurang bertindakbalas dan memerlukan dos rawatan yang lebih tinggi jika dibandingkan dengan populasi secara umum. Sehingga ini, belum ada sebarang kajian yang secara khusus menilai kesan Alprostadil dikalangan pesakit kencing manis.

Kajian ini menilai keberkesanan dan keselamatan rawatan Alprostadil secara intrakavernosa khusus bagi pesakit kencing manis yang mengalami kegagalan ereksi. Kami juga menilai taraf kepuasan pesakit berdasarkan indeks antarabangsa fungsi ereksi, iaitu suatu soal selidik yang mengemukakan 15-soalan yang telah dipersetujui di peringkat antarabangsa dan pengumpulan maklumat tentang tabiat seksual pesakit sebulan selepas tamat tempoh rawatan.

Kajian kami merupakan kajian label terbuka dibahagikan kepada dua fasa iaitu; fasa peningkatan dos secara berperingkat yang dilakukan di klinik diikuti oleh fasa rawatan kesinambungan yang dilakukan sendiri oleh pesakit bagi tempoh 12 minggu di rumah. Suatu temuramah di adakan 4 minggu selepas tamat tempoh rawatan untuk mengumpul maklumat tabiat seksual pesakit.

30 pesakit kencing manis mengambil bahagian dalam kajian ini. Purata umur mereka ialah 55.8 ±8.1 tahun dan purata jangkamasa penyakit kencing manis ialah 11.1 ±5.4 tahun manakala purata tempoh kegagalan ereksi ialah 3.1 ±2.9 tahun. Secara keseluruhannya, 75% peratus pesakit berjaya mencapai tindakbalas penuh kepada rawatan. Purata dos berkesan diawal kajian adalah 21.5 ±12 ug. Purata dos muktamad yang digunakan adalah 26.4 ±14.2 ug. Purata tempoh untuk mula berkesan ialah 11.8 ±6.7 minit manakala tempoh kesan ereksi ialah 63 ±35.8 minit. 95% dari pesakit mencapai kepuasan berjimak semasa fasa kesinambungan. Indeks fungsi zakar antarabangsa menunjukkan keupayaan mencapai ereksi dan pengekalan tahap ereksi sewaktu berjimak. Sembilan orang pesakit telah menarik diri dalam masa kajian ini. Sebab-sebab penarikan diri termasuk; rawatan tidak berkesan (3), kesan

sampingan (3), penyelewengan protocol (1), gagal hadir untuk lawatan susulan (1) dan masalah dengan pasangan (1). Kesan samping yang paling kerap di hadapi ialah kesakitan ringan pada batang zakar. Sewaktu temuramah selepas tempoh rawatan, kekerapan berjimak dan kualiti kepuasan seksual di dapati tidak berubah berbanding dengan sebelum mulakan rawatan.

Sebagai rumusan, Alprostadil secara intrakavernosa adalah berkesan dan selamat digunakan untuk rawatan kegagalan ereksi akibat penyakit kencing manis; sekiranya dos Alprostadil di sesuaikan dengan peningkatan berperingkat mengikut keperluan individu dan pesakit mendapat pendidikan dan latihan yang secukupnya dalam penggunaan rawatan injeksi.

ABSTRACT

Erectile dysfunction is a common complication of Diabetes Mellitus. Intracavernosal Alprostadil, the naturally occurring form of Prostaglandin E_1, has been used successfully in the treatment of erectile dysfunction. Results with Alprostadil have shown a poorer response, shorter duration of action and need for higher dosage in diabetic patients with erectile dysfunction when compared to the general population. No study targeted specifically to the diabetic population has been completed with Alprostadil so far.

We thus set out to investigate the efficacy and safety of intracavernosal Alprostadil in diabetic patients with erectile dysfunction. We also assessed the quality of life of patients using the international index of erectile function, a validated 15-point questionnaire and gathered information about their sexual life one month after the end of treatment.

It was an open-labelled study with a dose titration phase done at the clinic followed by a maintenance phase of self-injection treatment lasting 12 weeks in the patient's home. An interview was conducted with the patient, 4 weeks after the end of treatment to gather information related to the patient's sexual life.

Thirty diabetic patients with stable partners and erectile dysfunction of at least 4 months duration were enrolled into the study. The mean patient age was 55.8 ±8.1 years, mean duration of diabetes was 11.1 ±5.4 years and mean duration of erectile dysfunction was 3.1 ±2.9 years. The overall response rate was 75% for full and adequate erections. Mean effective dose was 21.5 ±12 ug. Mean end point dose was 26.4 ±14.2 ug. Mean latent period was 11.8 ±6.7 minutes and mean duration of erection was 63 ±35.8 minutes. Satisfactory intercourse was possible in 95% of the injections during the home maintenance phase. Mean international index of erectile function questionnaire scores to questions assessing the ability to achieve and maintain erections demonstrated statistically significant improvements. A total of 9 patients were withdrawn during the trial. Causes of withdrawal included lack of efficacy (3), adverse event (3), protocol

violation (1), failure to follow up (1) and problems with partner (1). The most common adverse event reported was penile pain, which was mostly mild burning sensation. Other adverse events recorded include injection site haematoma, prolonged erection, and priapism. No significant changes in frequency and quality of sexual activity were observed during the post study interview when compared with prior to initiation of therapy.

In conclusion intracavernosal Alprostadil is efficacious and safe in the treatment of diabetic erectile dysfunction if the therapeutic dose of Alprostadil is defined by careful titration for each patient and if the patient receives proper education and training in the self-injection technique.

1 INTRODUCTION

1.1 Physiology of Erection

1.1.1 Haemodynamics

Penile erection is a neurovascular event modulated by psychological factors and hormonal status (Krane *et al.,* 1989). On sexual stimulation, nerve impulses cause the release of neurotransmitters from the cavernous nerve terminals and of relaxing factors from the endothelial cells in the penis, resulting in the relaxation of smooth muscle in the arteries and arterioles supplying the erectile tissue and a several fold increase in penile blood flow (Lue *et al.,* 1987). At the same time, relaxation of the trabecular smooth muscle increases the compliance of the sinusoids, facilitating rapid filling and expansion of the sinusoidal system. The subtunical venular plexus is thus compressed between the trabeculae and the tunica albuginea, resulting in almost total occlusion of venous outflow (Fournier *et al.,* 1987). These events trap the blood within the corpora cavernosa and raise the penis from a dependant position to an erect position, with an intracavernous pressure of approximately 100mmHg (the phase of full erection)(Lue *et al.,* 1983).

During sexual intercourse, the bulbocavernous reflex is triggered, the ischiocavernous muscles forcefully compress the base of the blood-filled corpora cavernosa and the penis becomes even harder, with the intracavernous pressure reaching several hundred millimetres of mercury (the phase of rigid erection). During this phase, the inflow and outflow of blood temporarily cease (Lue *et al.*, 1983). Detumescence can be the result of a cessation of neurotransmitter release, the breakdown of second messengers by

phosphodiesterases, or sympathetic discharge during ejaculation. Contraction of the trabecular smooth muscle reopens the venous channels, the trapped blood is expelled, and flaccidity returns. (Banya *et al.,* 1989)

1.1.2 Neurophysiology

Autonomic and somatic nerves innervate the penis. In the pelvis, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa, corpus spongiosum, and glans penis to regulate blood flow during erection and detumescence (Walsh *et al.*, 1982). The somatic component, the pudendal nerve, is responsible for penile sensation and the contraction and relaxation of the extracorporeal striated muscles (bulbocavernous and ischiocavernous).

There are three distinct types of erection in man, namely 'reflex', 'psychogenic' and 'nocturnal' (Andersson *et al.,* 1995). Reflex erections can be induced by manual stimulation of the penis. This response is abolished by damage to the sacral spinal reflex. All normal men experience nocturnal erections. Most are associated with rapid eye movement sleep. It is generally assumed that the presence of normal nocturnal erections indicates a diagnosis of psychogenic impotence (Seagraves *et al.*, 1987). Erotic stimuli induce psychogenic erections. The stimuli may be visual, olfactory or imaginative and the mechanisms are thought to involve both parasympathetic and sympathetic neural pathways. There appears to be a synergy between reflex and

psychogenic erections such that erotic visual or imaginative stimuli improve the response to manual stimuli and vice versa (Melman *et al.*, 1988).

The maintenance of the intracorporeal smooth muscle in a semicontracted state i.e., penile flaccidity results from three factors: intrinsic myogenic activity, adrenergic neurotransmission, and the endothelium-derived contracting factors such as prostaglandin $F_{2\alpha}$ and endothelins (Saenz *et al.*, 1989a).

Nitric oxide released during nonadrenergic neurotransmission and from the endothelium is probably the principal neurotransmitter mediating penile erection (Saenz *et al.*, 1989b). Within the muscle, nitric oxide activates a soluble guanyl cyclase, which raises the intracellular concentration of cyclic guanosine monophosphate (GMP). Cyclic GMP in turn activates a specific protein kinase, which phosphorylates certain proteins and ion channels, resulting in the opening of potassium channels and hyperpolarisation of the muscle cell membrane, sequestration of intracellular calcium by the endoplasmic reticulum, and blocking of calcium influx by the inhibition of calcium channels (Burnett, 1997). The consequence is a drop in cytosolic calcium concentrations and relaxation of the smooth muscle. During the return to the flaccid state, cyclic GMP is hydrolysed to GMP by phosphodiesterase type 5. Other phosphodiesterases are also found in the corpus cavernosum, but they do not have an important role in erection (Burnett, 1997). Communication among smooth-muscle cells takes place through gap junctions in the membrane of adjacent cells, which allow the passage of ions and second messengers to synchronize muscle activity (Christ *et al.*, 1993).

1.2 Introduction to Erectile Dysfunction

For many men, life without sex can be likened to a water colour painting that should possess all of the vibrant colours of life but which has been reduced to sterile black and white. Although regarded as a benign disorder erectile dysfunction (ED) has a profound effect on the quality of life of many men. ED impairs sexual performance, diminishes self-esteem and disrupts personal relationship (NIH Consensus, 1993).

1.3 Definition

'Erectile Dysfunction' (ED), is defined by the National Institute of Health Consensus Panel on Impotence as the persistent inability to attain and maintain an erection sufficient to perform satisfactory sexual activity (Benet *et al.*, 1995).

1.4 Epidemiology

The prevalence of ED in the community as a whole is not well documented. This is largely due to variability in the definition of ED and the fact that most studies include very selected populations. Estimates suggest, that between 20 and 30 million men are affected in the United States alone (Benet *et al.*, 1995; Feldman *et al.*, 1994). Based on the data from United States, if the incidence were, of the order of 10% in the general population, there would be some 1 million men in Malaysia suffering from ED.

1.5 Aetiology

Broadly speaking, ED can be defined as being the consequence of either organic or inorganic (i.e. psychogenic) disease. It may result from psychological, neurologic, hormonal, arterial, or cavernosal impairment or from a combination of these factors. Erectile failure is commonly due to a complex interaction between psychological and physical problems. In younger men psychological causes predominate, whilst in men aged over 50 organic causes are more common. A wide range of systemic diseases are associated with ED.

1.5.1 Diabetes Mellitus

A common complication of diabetes mellitus in men is ED. It occurs at an earlier age in diabetics than in the general population. In the Massachusetts Male Ageing Study (Feldman *et al.*, 1994), the age adjusted prevalence of complete ED (no erection) was 28% in treated diabetics. The prevalence of complete ED in men attending diabetic clinics was approximately 3 times higher than that observed in the entire sample of men (10%). The prevalence of ED in Diabetics has been reported to increase from 15% at age 30-34 years to 55% at age 60 years (Smith, 1981). Characteristically, ED develops 10-15 years earlier in the diabetics than in non-diabetic patients (Lehman *et al.*, 1983). This effect is related both to age and the severity of the diabetes, assessed by dependence on treatment and presence of other diabetic complications. ED in men with diabetes is often associated with diabetic neuropathy and peripheral vascular disease.

1.6 Pathophysiology of Erectile Dysfunction

Erectile dysfunction can be classified as psychogenic, organic (neurogenic, hormonal, arterial, cavernosal, or drug-induced), or mixed psychogenic and organic (Table 1.1).

1.6.1 Diabetes Mellitus

In most patients, the ED develops during the course of the disease, but in a small proportion, it may be the presenting feature. Most reports indicate that there is no difference in incidence between those who are treated with oral hypoglycaemics and those who require insulin. It has been suggested that the likelihood of developing ED be related to the degree of glycaemic control (McCulloch *et al.*, 1980).

The pathophysiology of ED in diabetes is multi-factorial, and the roles of neuropathy and arteriopathy are well recognised (Table 1.2). Diabetes can cause an autonomic neuropathy that may lead to ED, and it can also accelerate the development of atherosclerosis. Diabetes leads to abnormal endothelial and smooth muscle function throughout the body, and in the penis this can lead to ED (Whitehead *et al.*, 1990).

Table 1.1 Classification and common causes of erectile dysfunction

Category of ED	Common Disorders	Pathophysiology
Psychogenic	Performance anxiety Relationship problems Psychological stress Depression	Loss of libido, over inhibition, or impaired nitric oxide release
Hormonal	Hypogonadism Hyperprolactinemia	Loss of libido and inadequate nitric oxide release
Vasculogenic (arterial or cavernosal)	Atherosclerosis Hypertension Diabetes mellitus Trauma Peyronie's disease	Inadequate arterial flow or impaired veno-occlusion
Neurogenic	Stroke or Alzheimer's disease Spinal cord injury Radical pelvic surgery Diabetic neuropathy Pelvic injury	Failure to initiate nerve impulse or interrupted neural transmission
Drug- induced	Antihypertensive and antidepressant drugs Antiandrogens Alcohol abuse Cigarette smoking	Central depression Decreased libido Alcoholic neuropathy Vascular insufficiency
Caused by other systemic diseases and ageing	Old age Diabetes mellitus Chronic renal failure Coronary heart disease	Usually multifactorial, resulting in neural and vascular dysfunction

(Adapted from Lue T.F., 2000)

Table 1.2 Possible pathophysiological factors in diabetic erectile dysfunction

Neurogenic	Autonomic Neuropathy Peripheral Neuropathy
Arterial	Increased risk of atherosclerosis Microangiopathy
Endothelial	Impaired endothelial-dependant smooth muscle relaxation
Myogenic	Impaired smooth muscle function

(Adapted from Eardley *et al.*, 1998)

1.6.1.1 Neural factors

The neuropathy seen in diabetes initially affects small unmyelinated fibres which innervate the corpora cavernosa. In the later stages of the disease, larger myelinated fibres are also affected, producing the classic 'glove and stocking' distribution of peripheral neuropathy (Saenz *et al.,* 1988). At a cellular level, there is depletion of neurotransmitters including vasoactive intestinal polypeptide, acetylcholine and noradrenaline in association with reduced levels of nitric oxide (Saenz *et al.,* 1989b).

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1.6.1.2 Arterial factors

Diabetes mellitus is associated both with atherosclerosis in large arteries, which appears more frequently and at an earlier age than in non-diabetics, and with microangiopathy, characterised by increased thickening of the capillary basement membrane (Whitehead *et al.*, 1990). Duplex ultrasound scanning of the penile arteries has shown that, in impotent men, diabetes is associated with a smaller penile artery diameter and lower peak flow velocities following injection of an intracorporal vasoactive agent (Persson *et al.*, 1989). There is a close correlation between diabetic ED and other manifestations of diabetic vascular disease, namely retinopathy, intermittent claudication and the risk of amputation (McCulloch *et al.,* 1980). Any reduction in arterial flow to the penis will inevitably lead to ischaemic changes within the corpora.

1.6.1.3 Endothelial and myogenic factors

The endothelium lining the lacunar spaces is important in controlling corporal smooth muscle tone, as nitric oxide, constrictor prostanoids and endothelin are all produced there and act directly on the smooth muscle cell. In diabetes, there is impaired neurogenic and endothelium-dependent smooth muscle relaxation to acetylcholine (Saenz *et al.,* 1989a). There is an augmentation of the contractile response to adrenergic agonists and a reduced relaxation response to nitric oxide upon exposure to hyperglycaemia. There is also overproduction of oxygen free radicals such as the superoxide anion, which can occur in diabetes mellitus, leading to impaired cavernosal relaxation by inactivating nitric oxide (Rajfer *et al.,* 1992). A third explanation is that hyperglycaemia leads to induction of the enzyme aldose reductase and to an increased production of sorbitol, which in turn causes an increased consumption of NADPH, an essential co-factor in the production of nitric oxide (Burnett, 1997).

Advanced glycosylation end products (AGEs) have an important pathophysiological role in the complications of diabetes mellitus (Braunstein, 1997). AGEs are compounds, which are formed as a result of non-enzymatic reaction between glucose and the amino groups of long-lived tissue proteins such as collagen (Seftel *et al.*, 1997). They are found to occur in increasing amounts not only in association with diabetes but also with ageing. Amongst their various pathological effects that have been demonstrated is the ability to bind nitric oxide (Burnett, 1997).

It may be that in diabetes there is heightened contractility as well as decreased relaxation of the corporal smooth muscle. It is likely that the vascular and sinusoidal endothelium has a central role in the modulation of this process (Saenz *et al.*, 1989b).

1.7 Diagnosis of Erectile Dysfunction

1.7.1 Assessment of Erectile Dysfunction

When assessing the diabetic patient with ED, it is important to remember that in any one individual there may be a variety of etiological processes. Erectile dysfunction is occasionally the presenting symptom of a variety of diseases, such as diabetes mellitus, coronary artery disease, hyperlipidemia, hypertension, spinal cord compression, and pituitary tumour. Therefore, when a patient presents with ED, a thorough history (medical, sexual, and psychosocial) should be taken, the patient should undergo physical examination, and appropriate laboratory tests aimed at detecting these diseases should be performed. Erectile failure due to diabetes mellitus tends to have a gradual onset, whereas a sudden loss of erections suggests a psychosexual problem. A detailed psychosocial history may reveal deep-seated psychological problems or relationship conflicts that can be successfully treated only by mental health professionals. All drugs being taken and the duration of their treatment should be recorded. The physical examination should include evaluation of the breasts, hair distribution, penis, and testes; palpation of the femoral and pedal pulses; and testing of genital and perineal sensation. Particular attention should be paid to any signs of diabetic complications. Any

general physical disability must be noted including any problems with impaired mobility or manual dexterity, poor cognitive function or problems with vision. Any of this may not only impair sexual function but also be relevant to the planning of treatment. Recommended laboratory tests include urine analyses, a complete blood count, and measurements of serum glucose, creatinine, cholesterol, triglycerides, and testosterone while the patient is fasting. If the man's serum testosterone concentration is low, serum free (or bioavailable) testosterone, prolactin, and luteinizing hormone should be measured.

The physician should then assess the findings, inquire about the goals and preferences of the man (and his partner), discuss further diagnostic tests (Table 1.3) and therapeutic options (Table 1.4), and provide information on sexual physiology and pathophysiology so that the man's participation and that of his partner in the decision-making process will be well informed.

Table1.3 Specialised urologic and radiologic tests.

Test	Indications
Combined penile injection of a vasodilator and sexual stimulation	Assess penile vascular function Therapeutic test in men who choose intracavernous therapy
Duplex (color) ultrasonography	Assess vascular function and evaluate for Peyronie's disease
Cavernosography	Young men with traumatised or congenital venous leakage
Penile arteriography	Young men with traumatised arterial insufficiency
Nocturnal penile monitoring	Differentiate psychogenic from organic erectile dysfunction

(Adapted from Lue T.F., 2000)

Table 1.4 Treatment options

Treatment	Advantages	Disadvantages
Psychosexual therapy	Non invasive Partner involved Curative	Time consuming Patient resistance
Oral sildenafil	Oral dose Effective	Cardiovascular disease a contraindication in some men 1hour wait
Transurethral Alprostadil	Local therapy Few systemic side effects	Moderately effective Requires office training Causes penile pain
Intracavernous Alprostadil	Highly effective Few systemic side effects	Requires injection High dropout rate Can cause priapism or fibrosis Causes penile pain
Vacuum constriction device	Least expensive No systemic side effects	Unnatural erection Causes petechiae Causes numbness Trapped ejaculation
Surgical prosthesis	Highly effective	Unnatural erection Infection Requires replacement in 5-10 years Requires anaesthesia and surgery
Vascular surgery	Curative	Poor results in older men with generalised disease Requires anaesthesia and surgery

(Adapted from Lue T.F., 2000)

Some men may benefit from referral for further testing and treatment. The indications for referral to a specialist include complex gonadal or other endocrine disorders, a neurologic deficit suggestive of brain or spinal cord disease, deep-seated psychological or psychiatric problems, Peyronie's disease, post-traumatic or primary ED, and active cardiovascular disease, especially if the man wishes to take sildenafil. If primary hypogonadism is detected, androgen therapy is the treatment of choice. This approach to the diagnosis and treatment of ED is tailored to the individual man's health status and goals.

1.7.2 Scales for Erectile Dysfunction

ED scales are helpful to standardise the severity of patients' symptoms and to provide an objective measure of the effects of the various treatments. In general, these involve patients self-reporting on their sexual function by a series of questionnaires but it is essential that these be adequately validated and relatively easy to administer. Various such questionnaires have been described. A good example is the International Index of Erectile Function (IIEF) (Rosen *et al.*, 1997). This scale is based on a 15-item questionnaire, identifies five important domains, namely erectile function (six questions), orgasmic function (two questions), sexual desire (two questions), intercourse satisfaction (three questions), and overall satisfaction (two questions). This scale has been validated in studies of 351 men. This scale also has high sensitivity and specificity in monitoring effects of treatment. Its shortcomings are that it

concentrates only on erectile function and not on the other components of sexual function and that there is limited assessment of the partner.

1.8 Drug Therapy for ED

1.8.1 Androgen Replacement Therapy

In men with hypogonadism, oral testosterone preparations are less effective than intramuscular and transdermal testosterone preparations (Morales *et al.*, 1994; Arver *et al.*, 1996) and may be hepatotoxic (causing cholestasis, hepatitis, and benign or malignant tumors). Testosterone cypionate and testosterone enanthate are often used for replacement therapy; the usual dosage is 200 mg intramuscularly every two to three weeks. Their chief drawback is their roller-coaster effect: they have high activity the first week after injection, with a decrease thereafter (Morales *et al.*, 1994). Transdermal testosterone preparations are now available. Daily application of these preparations raises serum testosterone concentrations to within the normal range in over 90 percent of men (Arver *et al.*, 1996). The most common adverse effects are skin irritation and contact dermatitis. Because it stimulates growth of the prostate, androgen therapy is contraindicated in men with prostate cancer or obstruction of the bladder neck caused by prostate hypertrophy. In men receiving long-term testosterone therapy, the haematocrit and serum testosterone, lipids, and prostate-specific antigen should be measured every six months (Cooper *et al.*, 1996).

1.8.2 Oral therapy

Sildenafil

Sildenafil is a selective inhibitor of phosphodiesterase type 5, which inactivates cyclic GMP. When sexual stimulation releases nitric oxide into the penile smooth muscle, inhibition of phosphodiesterase type 5 by sildenafil causes a marked elevation of cyclic GMP concentrations in the penis, resulting in increased smooth-muscle relaxation and better erection (Beavo, 1995). Sildenafil has no effect on the penis in the absence of sexual stimulation, when the concentrations of nitric oxide and cyclic GMP are low (Boolell *et al.*, 1996).

In clinical studies, the number of erections and the rates of penile rigidity, orgasmic function, and overall sexual satisfaction was significantly higher with sildenafil than with placebo (Goldstein *et al.*, 1998a). Most adverse events were mild to moderate and self-limited in duration (Goldstein *et al.*, 1998a). Adverse events include headache, flushing, dyspepsia, nasal congestion, and abnormal vision (described as a mild and transient colour tinge or increased sensitivity to light). The visual effect is probably related to inhibition of phosphodiesterase type 6 in the retina. No chronic visual impairment has been reported. Adverse cardiovascular events (nasal congestion, headache, and flushing) were mild and transient in the majority of men (Morales *et al.*,1998). However; because most of the studies excluded men taking nitrates and those with concomitant medical conditions, the incidence of serious cardiovascular events could be expected to be higher in the general population. Cardiovascular status should be carefully assessed before treatment. The combination of nitrates and sildenafil has resulted in severe hypotension and deaths (Cheitlin *et al.*, 1999).

Therefore, nitrate therapy is an absolute contraindication to sildenafil therapy. In response to the concern of physicians, the American Heart Association has published a guideline for sildenafil therapy (Cheitlin *et al.*, 1999). Sildenafil is absorbed well, and the plasma concentrations are maximal within 30 to 120 minutes (mean, 60). It is eliminated predominantly by hepatic metabolism, and the terminal half-life is about four hours. The recommended starting dose is 50 mg taken one hour before sexual activity. The maximal recommended frequency is once per day. On the basis of effectiveness and side effects, the dose may be increased to 100 mg or decreased to 25 mg (Goldstein *et al.*, 1998a; Marc *et al.*, 1999).

Yohimbine

Yohimbine is an α_2-adrenergic receptor antagonist. It presumably acts at the adrenergic receptors in brain centres associated with libido and penile erection. A meta-analysis of studies found that yohimbine was better than placebo for all types of erectile dysfunction combined. And its effect was most noticeable with respect to non-organic ED (Ernst *et al.*, 1998). The most frequently reported side effects are palpitation, fine tremor, elevation of blood pressure, and anxiety.

Phentolamine

Oral phentolamine has been reported to improve erectile function (Gwinup, 1988, Goldstein, 1998b). Side effects include headache, facial flushing, and nasal congestion.

Apomorphine

Apomorphine is a potent emetic that acts on central dopaminergic (D1 or D2) receptors. When injected subcutaneously, it induces erections but the side effects, notably nausea, seriously limit its clinical usefulness. A sublingual formulation of apomorphine is undergoing clinical trials (Padma *et al.*,1998).

Trazodone

Trazodone is a serotonin antagonist and reuptake inhibitor, used as a sedative and antidepressant, which causes priapism in rare cases. Its effect on erection is thought to be the result of serotonergic and α-adrenolytic activity. Trazodone alone or in combination with yohimbine has been reported to improve erectile function in some men (Lance *et al.*, 1995; Montorsi *et al.*, 1994).

1.8.3 Transurethral Therapy

Prostaglandin E_1 is an endogenous unsaturated 20-carbon fatty-acid derivative of arachidonic acid, and Alprostadil is a more stable, synthetic form of prostaglandin E_1. Transurethral Alprostadil was effective in 43 percent of men with erectile dysfunction from various organic causes (Padma *et al.*, 1997; Wolfson *et al.*, 1993). The advantages include local application, minimal systemic effects, and the rarity of drug interactions. The major drawbacks are moderate-to-severe penile pain, a low response rate, and inconsistent efficacy (Wertman *et al.*, 1997).

The first application (usually a 500 μg dose) should be undertaken in the physician's office because of the potential complications of urethral bleeding, vasovagal reflex, hypotension, and priapism. Depending on the erectile response, the man can then be instructed to increase or decrease the dose (up to 1000 μg or down to 250 μg) (Padma *et al.*, 1997).

1.8.4 Intracavernous Therapy

The introduction of intracorporal injection therapy in the early 1980s revolutionised the treatment of ED as it was the first means of providing safe and effective treatment for men with erectile difficulties (Brindley, 1983; Virag, 1982). The next significant advance occurred in 1986 when the first results of injecting prostaglandin E_1 (PGE_1) into the penis were reported. It soon became clear that the use of PGE_1 led to improved efficacy and was associated with a reduction in side effects (Stackl *et al.*, 1988).

These compounds produce an erection by their action upon the penile smooth muscle. Although the compounds used in intracorporal injection may exert effects on smooth muscle throughout the body, the doses required to produce erections are so small that they rarely cause systemic side effects when injected into the penis. The method of administration directly into the penis allows good local concentrations to be achieved with small doses, with minimal spill into the general circulation (Virag, 1982).

The most commonly used intracavernous drugs are alprostadil and a combination of papaverine, phentolamine, and alprostadil (trimix) (Gupta *et al.*, 1997).

Papaverine

Papaverine is a phosphodiesterase inhibitor that increases cyclic AMP and cyclic GMP concentrations in penile erectile tissue (Stief *et al.,* 1988). The usual dose ranges from 15 to 60 mg. It is highly effective in men with psychogenic and neurogenic erectile dysfunction, but it is less effective in men with vasculogenic erectile dysfunction (Virag, 1982). Its advantages include low cost and stability at room temperature. Major disadvantages are priapism, corporal fibrosis, and occasional increases in serum aminotransferase concentrations (Stief *et al.,* 1988).

Phentolamine

Phentolamine is a competitive α-adrenergic receptor antagonist. Phentolamine produces erections when combined with papaverine (Stief *et al.*, 1988). Most urologists prescribe a combination of 30 mg of papaverine and 0.5 to 1 mg of phentolamine, and the usual dose ranges from 0.1 to 1 ml. The side effects of phentolamine include hypotension and reflex tachycardia.

Vasoactive Intestinal Polypeptide

Vasoactive intestinal polypeptide is a potent smooth muscle relaxant which when combined with phentolamine, produced erections sufficient for sexual

intercourse (Dinsmore *et al.*, 1998). Common side effects include transient facial flushing, bruising, pain at the injection site, and truncal flushing.

Alprostadil

Prostaglandin E_1 (PGE_1) is now the most commonly used single agent for intracorporal injections. It has achieved this dominance because of its efficacy and safety, which are superior to all other single agents (Porst, 1996). It acts primarily via specific receptors on the surface of the smooth muscle cell to stimulate the enzyme adenylate cyclase (Linet *et al.*, 1994). This enzyme converts ATP to cyclic AMP (cAMP) and therefore injection of PGE_1 causes a rise in intracellular cAMP, which in turn results in a fall in intracellular calcium and smooth muscle relaxation. PGE_1 may also reduce the noradrenaline released from presynaptic noradrenergic nerve terminals, with the anticipated synergistic effects (Stackl et al., 1988).

Three formulations of alprostadil have been used for intracavernous injection: Prostin VR (Pharmacia & Upjohn), a paediatric formulation; Caverject (Pharmacia & Upjohn), a lyophilized powder; and Edex (Schwarz Pharma), which contains alprostadil in complex with α-cyclodextrin.

Alprostadil is the only intracavernous drug approved in the United States. Its efficacy is superior to that of papaverine and the combination of papaverine and phentolamine; it results in erections in more than 70 percent of men (Stackl *et al.*, 1988; Lee *et al.*, 1989).

In addition, Alprostadil is associated with a relatively low incidence of priapism and fibrosis (Porst, 1996).

The usual dose ranges from 5 to 20 μg. The most frequent side effect is painful erections (Porst, 1996). The hyperalgesic effect is more prominent in men with partial nerve injury, such as those with diabetic neuropathy.

Although the response rate is high, in long-term studies 38 to 80 percent of men ceased therapy (Weiss *et al.*, 1994; Gupta *et al.*, 1997). There are several published reports on the use of Alprostadil in diabetic patients. The success was lower in patients over 60 years of age and in patients with duration of diabetes longer than 10 years (Ishii *et al.*, 1986; Stackl *et al.*, 1988; Porst, 1996). No significant differences were found between the diabetics and non-diabetics in terms of satisfaction with the injection technique and in adverse reactions. The diabetics had a significantly shorter duration of erection (Linet *et al.*, 1994; Stackl *et al.*, 1988). Some men alternate injection therapy with sildenafil or transurethral alprostadil, preferring injection when an erection of longer duration is desired.

1.8.5 Transdermal Medications

Nitroglycerin cream or paste, alprostadil cream, and a cream containing aminophyline, isosorbide dinitrate, and co-dergocrine mesylate have been used in pilot studies in men with erectile dysfunction; the results have been mixed (Gomaa *et al.*, 1996).

1.9 Rationale for the study

A new formulation of PGE_1, namely Alprostadil Sterile Powder [S.Po.,CAVERJECT®] has been developed and investigated. Many clinical studies have been completed to evaluate the effectiveness and safety of Alprostadil in the treatment of ED (Stackl *et al.*, 1988; Lee *et al.*, 1989; Linet et al., 1994; Porst, 1996). A total of 1,712 men aged 20 to 79 years (mean, 54.9 years) with ED of vasculogenic, neurogenic, psychogenic, mixed, or unknown aetiology have received intracavernosal treatment with Alprostadil in these studies and 280 patients were injected with placebo. Based on the results of these trials, it was concluded that if the therapeutic dose of Alprostadil is defined by careful titration for each patient and if the patient receives proper education and training in the self-injection technique, Alprostadil is an effective and safe treatment for ED.

Patients with diabetes mellitus required somewhat higher doses of Alprostadil to achieve a response and a lesser number of diabetic patients responded to Alprostadil than patients without diabetes (Burgess *et al.*, 1990). The mean optimum dose for diabetic patients was 21.5 μg while the mean optimum dose for non-diabetic patients was 17.4 μg. Response rates were 76% (115/152) for diabetic patients and 87% (598/684) for non-diabetic patients.

No study targeted specifically to the diabetic population has been completed with Alprostadil so far. The purpose of this study was to gain experience with Alprostadil in Malaysian diabetic patients with ED. Information was gathered about the sex life of the patient one month after the end of treatment and an