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Drug Treatment of Nocturnal Enuresis

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Abstract

Primary nocturnal enuresis is a common condition affecting about 500,000 children in the United Kingdom. It is a distressing condition for which a pathological cause is rarely found. Treatment for this condition should be tailored to individual patients after a thorough assessment. The treatment options available are behavioural measures, including enuresis alarms, and pharmacological intervention. Enuresis alarms are the most effective treatment, but drug treatment provides a valuable adjunct to this, especially in refractory cases, or when behavioural treatments are not practicable. This review will mainly focus on the drug treatments currently in use.

Key words: Enuresis – Desmopressin – Tricyclics – Oxybutinin

Introduction

Nocturnal enuresis is defined as wetting at night, in a child over five years, in the absence of neurological or structural problems affecting the bladder. It is a common condition, with a prevalence of 15–20% of five-year olds, decreasing to 5% of ten-year olds and 1–2% of those over 15 years[1,2]. There is a spontaneous cure rate of about 15% per year in children aged 5–18 years[3]. Although many children would stop bedwetting without intervention, treatment is justified when the child and family are distressed by the wetting and when the wetting is associated with a loss of self-esteem and confidence[4,5]. There is some evidence that successful treatment not only improves the wetting, but may also improve self-esteem as well[6,7]. There are a number of effective interventions available to children and their parents, including behavioural measures, alarm treatment and pharmacological approaches, and one role of the health professional is to help tailor the treatment to suit the individual's circumstances.

The evaluation of a child with nocturnal enuresis should start with consideration of possible organic causes such as urinary tract infection, neuropathic bladder, or polyuric states. These organic causes are, however, rarely found. In all patients a detailed history and examination, including growth parameters and blood pressure, is essential. Urinalysis should be performed on a clean urine sample, and the urine should also be sent for microscopy and culture. These tests are usually all that is indicated in an otherwise well child with a normal clinical examination. A child with associated daytime symptoms may need more detailed investigation, particularly if urinary tract infection is present[8,9]. A psychosocial history is also important as it may reveal factors responsible for the wetting, while in other instances it may reveal the impact that the wetting is having on the family[10].

Aetiology of Primary Nocturnal Enuresis

The aetiology of nocturnal enuresis is not fully understood and several factors are likely to contribute to its pathogenesis. There has been considerable progress in the understanding of a number of contributory factors including genetic ones, decreased functional bladder capacity or abnormal bladder function, nocturnal polyuria, sleep disorders and psychological ones.

Genetic Factors

A genetic predisposition has been suggested by the high familial incidence, and is also supported by twin studies[11]. There is about a 40% chance of a child having nocturnal enuresis if one parent had the condition[12] and 75% of children with enuresis have a first-degree relative who has, or has had, primary nocturnal enuresis. Recent studies in affected families suggest genetic linkage to chromosomes 13q[13] and 12q[14], work continues to try to identify other important loci.

Bladder Capacity and Function

It seems that most bedwetters have normal bladder volumes and there is little evidence to suggest bladder instability as the primary cause in the absence of daytime symptoms[15,16]. There are some studies using urodynamic evaluation which demonstrate a high incidence of bladder instability – particularly in those who don't respond to first-line treatments[17].

Nocturnal Polyuria

There is evidence that many affected individuals have relative nocturnal polyuria with an absence of the normal increase in secretion of antidiuretic hormone (ADH) at night[18,19]. This does not, however, explain why they fail to wake to empty their bladders.

Sleep/Arousal State

There is anecdotal evidence that some bedwetters are more difficult to rouse – in particular parents find affected children seem to sleep more heavily than siblings who do not suffer from enuresis[20]. Wolfish found arousal from sleep more difficult in enuretic children than age-matched controls[21]. However, other studies have not demonstrated any difference in sleep patterns of those affected, and healthy controls and enuresis has been shown to occur in any stage of sleep and that it is not just localised to the periods of deepest sleep[22]. Enuresis has been identified in some adults and children with sleep apnoea. It is difficult to know the relevance of this to sleep patterns or bladder function, but there are some cases of the resolution of nocturnal enuresis after adenotonsilectomy in children with a history suggestive of upper airways obstruction at night[23].

Psychological Factors

Psychological disturbances are undoubtedly more common among children with enuresis, but this is most marked in those with daytime wetting and secondary onset enuresis. Among those with primary monosymptomatic nocturnal enuresis, the majority of children have no psychological disorder. It is often difficult to determine whether psychological problems are the cause of, or result of, the enuresis. Nonetheless, 'stressful life events' in young children are associated with an increased incidence of enuresis.

At present one can only speculate as to how the various factors interrelate. It seems likely that many children are genetically susceptible to delayed acquisition of dryness at night, and that certain trigger factors, such as stressful events, may also intervene, and that these factors alter bladder function, ADH secretion or sleep arousability, resulting in nocturnal enuresis.

Treatment

This should be individually tailored and requires explanation, information and reassurance[24]. Behavioural methods, in particular, need considerable motivation and enthusiasm to be successful. In general, children under five years do not require treatment other than explanation, reassurance and practical advice for parent and child. For children between five and seven years, star charts, rewards and positive reinforcement may be the first line, and occasionally medications or alarms may be used. In those over seven years the choice of treatment usually lies between alarms and drug treatment as the enuresis is likely to be more distressing and will be impacting on the child's social life. Enuresis alarms can be used in younger children, but are more difficult to use, as the children lack the necessary motivation and understanding of the treatment.

Overall alarm treatments have undoubtedly the highest cure rates and the lowest relapse rate, but may not always be appropriate, particularly if rapid dryness is needed[25]. Many drug treatments have been tried in the past to treat bedwetting. At times, it has been difficult to determine whether improvement is due to the pharmacological action or the placebo effect. Clearly it is important that drugs are evaluated with other treatment options within the setting of randomised controlled trials. In this review we are therefore only going to discuss drugs for which there is reliable evidence of efficacy from randomised controlled trials.

Desmopressin (DDAVP)

Mechanism of Action

DDAVP (1-deamino-8-D-arginine vasopressin) is a synthetic analogue of human arginine vasopressin (AVP) and acts by binding V2 receptors in the renal tubules and collecting system, leading to an

increase in water permeability, and thus water reabsorption, leading to smaller volumes of more concentrated urine being produced. Unlike endogenous AVP, DDAVP has little vasoactive action (V1 receptor mediated)[26–28]. Although it has been used empirically since the late 1960s, more recent studies suggest a physiological rationale for its use – a relative decrease in nocturnal ADH secretion is a factor in some bedwetters[18,19]. This drug has other actions – in particular at high concentrations it causes a rise in plasma Factor VIII levels. The mechanism for this is still not known, but there is some data supporting the theory that it induces the release of Factor VIII:RC from the endothelium. DDAVP also liberates plasminogen activator from the endothelium[29,30].

Pharmacokinetics/Pharmacodynamics

DDAVP is available both as a nasal spray and in tablet form. Both formulations have been compared in double-blind crossover trials and have been shown to be equally effective[31]. Although only about 10% of a nasal dose is absorbed, it is absorbed quickly and reaches maximum plasma concentration about 40–55 minutes after dosage. Its half-life is 4–6 hours with a duration of action of around 10–12 hours[32]. There is no data on the relationship between plasma concentration of DDAVP and effect. There is thus no clinical value in measuring plasma concentration. AVP is degraded principally by the liver, kidney, brain and within plasma, and DDAVP is probably eliminated in a similar way. The drug is much more resistant to enzyme degradation and so has a very much longer half-life than endogenous AVP. There is no evidence of pharmacologically active metabolites.

Effectiveness

DDAVP is a potent antidiuretic and improves bedwetting in 65–80% of patients[33,34]. Those who do not respond may have a different pathophysiology to their bedwetting, or different pharmacokinetics or pharmacodynamics[34]. The reported effectiveness of desmopressin varies considerably between trials: Moffatt *et al.*[35] found a reduction in wet nights in about 70%, but less than 30% became completely dry on medication. Other studies have reported between 10% and 40% completely dry on treatment. A recent systematic review of interventions for enuresis from the NHS Centre for Reviews and Dissemination concluded that DDAVP, at a dose of 10 mcg, resulted in two fewer wet nights per week (on average) than placebo, and those treated with DDAVP were 4.5 times more likely to have 14 consecutive dry nights than placebo[25]. When treatment is stopped, however, DDAVP-treated patients had no more dry nights than the placebo treated, thus demonstrating no lasting benefit. DDAVP has been compared directly with alarm treatment in two studies. Generally, there is a faster initial response (in the first three weeks) with DDAVP, but a much higher relapse rate when drug treatment is withdrawn. Relapse rates after a treatment period on DDAVP are > 70% and with alarms only about 30%[36,37]. If a fast response is needed, DDAVP has advantages over alarm treatment, but patients must be warned of the high relapse rate when medication is discontinued. One encouraging development is the combining of DDAVP with the enuresis alarm. This may allow the short-term benefits of the drug to facilitate the use of the alarm, resulting in improved long-term outcome.[38]

Which Patients?

DDAVP is indicated for the treatment of nocturnal enuresis as a single agent, or in combination with behavioural and alarm treatments. It is also effective if used episodically, for short-term treatment, when dryness is needed for special occasions such as holidays. There is expanding information about pretreatment prediction of which patients will respond to DDAVP[39]. It seems clear that those with less severe enuresis respond better. Also, those with large functional bladder capacities and those with primary, rather than secondary, enuresis have higher response rates[35]. The evidence is conflicting for many other variables. For example, Post *et al.*[40] demonstrated DDAVP to be more effective in older children; this finding has not been confirmed in other studies[33,41], nor does the sex of the child seem to predict treatment outcome. Unfavourable social and psychological factors are associated with treatment failure.

Dosage

The starting dose for the spray is 20 mcg at night (0.2 mg for the tablets). This starting dose is used irrespective of the age of the child. The dose can be doubled if there is a poor response to the lower dose. DDAVP can initially be prescribed for three months to assess initial response[32,42]. It can be used for much longer periods if successful. Clearly though, intervals off the treatment are needed from time to time to see if the child has become dry.

Side-effects/Drug Interactions

DDAVP is well tolerated with few side-effects[43]. It is a powerful antidiuretic and so there is a danger of fluid overload and severe hyponatraemia if fluid intake is too high. Indeed, there are several case reports of hyponatraemic convulsions, and cerebral oedema, related to this. Patients should be told

about fluid overload and advised to avoid excessive fluid intake in the evening or overnight. Mild hyponatraemia may develop in 1–10% of patients on DDAVP for primary enuresis, although this is usually asymptomatic[44]. Other uncommon side-effects include headaches, nausea and abdominal pain – these could possibly be related to hyponatraemia. The most common side-effects of nasal spray were nasal irritation and nosebleeds, but since a change in formulation this is now very unusual. The report in 1995 of the Swedish Enuresis Trial (SWEET) found that few side-effects were reported, with minor side-effects in 2.5% of patients[45].

In summary, DDAVP, nasally or orally, is safe and well tolerated. It improves wetting in the majority and enables a minority of children to be dry, but relapse is likely when treatment is withdrawn unless spontaneous resolution of enuresis has occurred.

Tricyclic Antidepressants

Mechanism of Action

Imipramine is the most commonly used drug in this group. Its mode of action remains uncertain although it is likely that the anticholinergic effects are important. These effects are not the whole answer as pure anticholinergic medications are not so successful. Imipramine acts on the central nervous system as a noradrenaline and serotonin reuptake inhibitor, and seems to have central effects on sleep level and perception – making arousal from sleep with a full bladder more possible[2]. In addition, it has an antidiuretic effect.

Pharmacokinetics/Pharmacodynamics

Imipramine is rapidly and completely absorbed orally. There is first pass metabolism in the liver to an active metabolite – desmethylimipramine[46,47]. About 90% of imipramine binds plasma proteins, and plasma levels of the drug correlate well with those in cerebrospinal fluid[48]. It is metabolised in the liver largely by demethylation. About 80% of the drug is excreted in the urine (mainly as active metabolites), with some in the faeces. The mean half-life is about 18 hours, with significant variation among patients[49].

Effectiveness

There is wide experience with this drug, and studies of its efficacy have been published since the 1960s. In the short term, imipramine leads to resolution of symptoms in 43–50% on treatment[50,51] but, as with DDAVP, there is a high relapse rate of > 70% off treatment. In a placebo-controlled trial, Smellie *et al.*[52] found an improvement in 72% of those taking imipramine (compared with 38% with placebo). Only 57% of those on imipramine had a continued improvement two months after treatment stopped[52]. The recent NHS Centre for Reviews and Dissemination concluded that patients treated with imipramine had 1.3 fewer wet nights per week than placebo and were four times more likely to attain 14 consecutive dry nights[25]. There were no eligible trials in the review, which reported on outcome after treatment is withdrawn. However, other reports clearly indicate a very high relapse rate. Overall there is no significant difference in the clinical outcomes in the trials of imipramine and the trials of DDAVP, but there have been no large-scale trials comparing the two drugs directly.

Which Patients

Imipramine is licensed for the treatment of nocturnal enuresis in children over six years. Although cheaper than DDAVP and probably of similar effectiveness overall, most practitioners do not use it as the first-line drug because of its unfavourable side-effect profile (see below).

Dosage

The dose of imipramine is age/weight determined and should not exceed 2.5 mg/kg. It should be taken as a single dose at bedtime. It is often most effective taken two to three hours before bedtime, particularly if wetting occurs in the first few hours of sleep. The maximum period of treatment should not exceed three months (including slow withdrawal)[42].

Side-effects/Drug Interactions

Imipramine has many more potential side-effects than DDAVP. Tricyclics have anticholinergic effects and antihistaminic effects, as well as α_2-adrenergic receptor blockade. This mixture of actions contributes to the variety of side-effects. These include anticholinergic side-effects, such as dry mouth, constipation, visual disturbance and urinary retention. Central side-effects, such as nausea, tremor, confusion, insomnia, agitation or sedation, are also reported, as well as disturbance in cognitive function[53]. The major concern, however, with this group of drugs is accidental poisoning[54]. Tricyclics are clearly cardiotoxic and potentially lethal in overdose, but there is little hard evidence of danger at therapeutic doses used in enuresis. Fletcher *et al.*[55] looked at 25 children taking imipramine and found ECG changes, including increased resting heart rate and a lengthening of PR interval. The changes were not felt to be clinically significant. Other studies have not demonstrated ECG changes. ECG monitoring

is recommended only for high-dose therapy[56–58].

There are important drug interactions with tricyclic antidepressants. There have been a number of reports of symptomatic hyponatraemia in children given both imipramine and DDAVP. As imipramine binds strongly to plasma proteins, its effects and side-effects may be increased by other drugs that bind albumin. Tricyclics are metabolised in the liver and so drugs that inhibit this metabolism (e.g. cimetidine, methylphenidate) may increase plasma levels. Tricyclics also inhibit hepatic metabolism of other drugs (e.g. warfarin) and so doses may need to be modified.

Imipramine is an effective, inexpensive, drug in the treatment of nocturnal enuresis. The potential side-effects, however, mean that many paediatricians have reservations about using it routinely. Other tricyclics, such as desipramine, amitriptyline and nortriptyline, have also been used successfully, but there is less experience with them, and they seem to have similar side-effect profiles to imipramine.

Oxybutynin

Oxybutynin is not established in the treatment of primary nocturnal enuresis as a single agent. In fact, studies have failed to demonstrate a positive effect above placebo in monosymptomatic nocturnal enuresis[59]. It does appear to have a role in nocturnal enuresis when there are significant daytime symptoms suggesting bladder instability.

Mechanism of Action

Oxybutynin is an anticholinergic drug and also has a direct antispasmodic action on smooth muscle inhibiting bladder contractions. It also has local anaesthetic properties. It should help by increasing bladder volume and reducing detrusor contractions during storage.

Pharmacokinetics/Pharmacodynamics

Oxybutynin is rapidly absorbed from the gastrointestinal tract and reaches maximum plasma concentrations in less than an hour. The maximum effect is seen within 3–4 hours, with some effect still evident at 10 hours.

Effectiveness

Previously, this drug has been useful in daytime wetting attributed to bladder instability, and recently an Italian multicentre trial has suggested that oxybutynin with DDAVP is more effective than DDAVP alone in treating nocturnal enuresis when there are daytime symptoms suggesting bladder instability, although details of the study are sparse. During treatment, patients with diurnal voiding disturbances and enuresis had a 71% 'success rate' with DDAVP and oxybutynin[60].

Which Patients

Oxybutynin is not recommended in the absence of daytime symptoms, but seems to have a role in those with refractory nocturnal enuresis who have significant daytime symptoms[60,61]. It is not licensed for use below five years.

Dosage

The usual starting dose is 2.5 mg 2–3 times daily – the last dose being given before bed. This dosage can be doubled if not beneficial at the lower dose[42].

Side-effects/Drug Interactions

Anticholinergic side-effects, such as dry mouth, constipation, blurred vision, nausea, abdominal pain and facial flushing, are common and were reported in 17% of children in one study[59]. The concurrent use of other drugs with anticholinergic side-effects should be avoided.

Conclusions

Primary nocturnal enuresis is a common condition and causes considerable distress to patients and their families. Treatment is warranted in those children upset by their symptoms in order to hasten a cure or to provide temporary respite. The mainstay of treatment remains explanation and reassurance, and behavioural measures including alarm treatment. Although alarms are the most effective treatment overall with better 'cure' rates (lower relapse rates off treatment) than drug treatments, there will still be many children for whom they are either not effective or not practicable at the current time. For these children drug treatments may be effective in the short term at least and may in some instances be successfully combined with the alarm[38]. DDAVP is the drug of choice for children with monosymptomatic nocturnal enuresis as it is effective at suppressing enuresis and has few side-effects. Children with enuresis who also have daytime symptoms of bladder instability (urgency and frequency) may benefit from the addition of oxybutynin as well. Tricyclics are a possible second-line drug but should be used with caution (and fully informed consent) because of their side-effects and toxic effects in overdose. Table 1 summarises and compares the current treatments that are available.

Table 1. Comparison of the available treatments for enuresis

Treatment	Dose	Success rate*	Comments
Enuresis alarm	–	60–80% dry, 20% relapse	Hard work, slow to work, best for motivated families
Dry bed training	–	80–90% success, relapse rate similar to alarm use	Intensive routine of waking, cleanliness training rewards and alarm – not for the the faint hearted – dryness achieved more rapidly than with alarm alone
Desmopressin	20–40 mcg nocte nasal spray 200–400 mcg	10–40% dry; up to 80% improve, but most will relapse	Hyponatraemia and water intoxication are rare adverse effects, therefore beware of excessive drinking. Good for short-term use
Tricyclic antidepressants	Starting dose 25 mg (< 11 years) or 50 mg (> 11 years)	Similar to desmopressin	Anticholinergic side-effects and mood changes common, and dangerous in overdose (cardiotoxicity). Interacts with many drugs Maximum duration of treatment three months
Oxybutinin	2.5 mg bd increased up to 5 mg tds	Inadequate data in the literature	Not usually effective on its own for bed wetting, anti cholinergic side-effects common. May help if bladder instability is present

*A wide range of results are reported in the literature reflecting the differing populations studied and varying methodologies

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