An Update on Pediatric Urology in Uppsala Sweden

FROM THE GUEST EDITOR

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Dear Friends and Colleagues,

It is a great honour for us to present the Pediatric Urology section of the University Children’s Hospital in Uppsala. It is an independent section within the Department of Pediatric Surgery with a close relations to the Departments of Urology, Pediatric Surgery and Pediatric Nephrology at the Akademiska Hospital. In Sweden, with a population of 9 million people, there are four centers of pediatric urology, Lund, Göteborg, Stockholm and Uppsala. Our department serves the large area of northern Sweden, with a population of 3 million people. At present there are four specialists in our section, Göran Läckgren, Arne Stenberg, Nils Wåhlin and Gillian Barker and one fellow, Erik Sköldenberg.

In this issue of Dialogues in Pediatric Urology we have the opportunity to present some of our ongoing clinical and experimental research projects in different fields of urology. Over the last 40 years our department has been involved in experimental and clinical research on the effect of obstruction of the upper urinary tract and most of the recent experimental work have been done by Arne Stenberg and Nils Wåhlin together with Prof. Erik Persson at the Department of Medical Cell Biology at Uppsala University.

This month the second combined meeting of the European Society of Pediatric Urology and the Urology Section of the American Academy of Pediatrics will be held in Uppsala, Sweden and hosted by the Pediatric Urology Section of the University Children’s Hospital in Uppsala. This has been an academic department that has been productive in many aspects of pediatric urology, both clinical and experimental. This issue provides us some insight to that productivity. Under the direction of Professor Göran Läckgren, Head of the Section of Urology at the University Children’s Hospital in Uppsala, this issue showcases the depth and breadth of clinical and experimental research. We are all familiar with the work from this institution on the endoscopic correction of reflux; however, other areas of contributions are equally important, such as the experimental model of upper urinary tract obstruction, angiogenesis and Wilms’ tumor, and the causes and treatment of nocturnal enuresis. All of these areas either have or will contribute to our understanding and knowledge in pediatric urology.

As the global world of pediatric urology continues to shrink with the advances in communication and sharing of information at combined international meetings, it is important for all of us to have an appreciation for the contributions of other sections of pediatric urology from around the world. The Editorial Board of the Dialogues in Pediatric Urology hopes to be able to showcase other institutions in a similar fashion.

My thanks to Professor Göran Läckgren and the members of his section of pediatric urology for this outstanding and enlightening issue.
Over recent years the endoscopic treatment of VUR has been an important alternative to both antibiotic prophylaxis and open surgery. This is the result of experimental research and the first clinical studies of a new substance, Deflux (dextranomer in hyaluronic acid), which was developed in Uppsala and that has proven to be safe with significant efficacy even after long-term follow-up. The new treatment policy is presented in this issue by Göran Läckgren and Arne Stenberg, who both have participated in the pioneering of this new substance.

In Uppsala the surgery of all retroperitoneal tumours have been managed by the pediatric urology section and we have participated in research projects on "the angiogenesis in Wilms’ tumour" in cooperation with the BioMedical Centre and the Department of Pediatric Surgery. The future aspects of this research is presented by Erik Sköldenberg and his tutor Rolf Christoffersson, scientist and pediatric surgeon.

The causes and treatment of nocturnal enuresis have been a research interest for 20 years, primarily by studying the effect of desmopression on monosymtomatic enuresis and later by the study of the sleep and arousal mechanisms of these children. The project has more and more focused on the bladder function in nocturnal enuresis and also on different combination treatment modalities of the non-responders to desmopressin or alarm. Most of this later work has been done by our pediatric nephrologist, Tryggve Nevéus, who is presenting some of our current ideas.

The incidence of UTIs post-treatment, particularly those affecting the upper urinary tract, is an important consideration. During our first 5 years’ follow-up of endoscopic injection, we found a strikingly low incidence of UTI (8%), and continued long-term monitoring of patient records has revealed very few cases of pyelonephritis. In the International Reflux Study (IRS), 22% of patients receiving antibiotic prophylaxis developed pyelonephritis within 5 years, compared with 8% of those who underwent ureteral reimplantation.10 The implication of these data is that endoscopic injection may minimize the risk of infections affecting the upper urinary tract, though further studies are needed to confirm this.

In recent years, injection techniques for patients with high-grade reflux have evolved, particularly intravesical injections in children with open orifices. The introduction of the hydrodistention-implantation technique (HIT) by Kirsch et al. in 200411 may further improve the overall cure rate. These data show minimal difference in success rate with the HIT between different grades of reflux,11 increasing the viability of endoscopic injection for grade IV–V reflux.

We believe that the injection into the ureteral orifice may decrease the risk of ‘bolus migration’ (distal, medial or lateral), one of the most common causes of failure with endoscopic injection. By adopting this approach we have significantly decreased the number of endoscopic treatments per patient, from 1.35 during our first 5 years to 1.24 during 1998-2003 (unpublished data). It must be pointed out that there is a definite learning curve with the injection technique that lasts for several years, particularly in severe cases and those with ureteral anomalies (double ureters or severely lateralized orifices).

VUR can occur alongside other anatomical anomalies, and the efficacy of endoscopic injection in complicated cases was, until recently, poorly documented. We treated a series of patients with VUR associated with double ureters (n=68) or a small kidney (n=40), using similar methodology to the unmodified STING.12 Among these patients, the positive response (reflux grade 0 or I post-treatment) was similar to that seen in uncomplicated cases. We further investigated the efficacy of NASHA/Dx gel in 50 children with VUR and concurrent bladder dysfunction (at least one of the following symptoms: high urinary urgency/frequency; day-time wetting or “lazy bladder”; poor emptying).13 The post-treatment VUR response rate was 82%, and this was accompanied by a rapid improvement in bladder dysfunction: 50% of the patients that were without reflux at the 3-month VCUG did not report any further symptoms of bladder dysfunction. This is particularly important, as it provides evidence that in some cases, VUR may be the cause of bladder dysfunction, and that primary treatment of VUR may be valuable. This is in contrast to the widely held view that bladder dysfunction is a contraindication to surgical correction of VUR.

Of particular interest are infants with severe reflux (grade V) where the bladder function may be effected by the high reflux volume. In those infants where the reflux does not resolve, bladder dysfunction is common.14 Is the reflux the cause of bladder dysfunction during the early maturation? If so, early treatment of reflux may improve maturation of bladder function, and, therefore, cure both reflux and bladder dysfunction.

Our data indicating the efficacy of NASHA/Dx gel endoscopic injection in complicated cases have been extended in another study.15 Seventy-two patients with a variety of complications were treated: failed open surgery, neurogenic bladder, double ureters, retained stump, Hutch diverticulum, ureterocele, ectopic ureter, posterior urethral valve, epispadias, urogenital sinus and prune belly syndrome. VUR was corrected in 68% of these cases after a single NASHA/Dx gel treatment.
Current practice and anticipated future directions

For a number of years we have been using NASHA/Dx gel injection as first-line treatment of persistent reflux. In view of the most recent data, we have extended the approach described in our published treatment algorithm such that we now only use open surgery as a second-line option. For children aged >12 months presenting with dilating VUR that is either persistent (>6 months, as shown by two positive VCUG tests) or high-grade (grade V), we generally recommend endoscopic injection with NASHA/Dx gel. For patients with grade I–II reflux, or even grade III with normal kidneys (i.e., no renal scarring or evidence of functional impairment) and without recurrent UTI, we often employ a policy of observation only with only short-term treatment in case of UTI (Figure 1). The rationale for this approach is based on a number of different considerations. Firstly, the likelihood of renal damage is lower with lower grades of reflux. Secondly, in the absence of renal scarring, justification for surgical intervention is arguably reduced. Thirdly, the benefits of long-term antibiotic prophylaxis are questionable, as UTIs occur in as many as 40% of children during 5 years treatment and the likelihood of antibiotic-resistant isolates is increased 23-fold among children treated on trimethoprim–sulfamethoxazole for >4 weeks. Also, in at least half of all VUR patients, antibiotic prophylaxis would be required for over 5 years before the condition resolves. Over time, therefore, we anticipate that the treatment approach described above will be used more widely.

Our current treatment practice reflects the changing perceptions of the need to treat VUR. With the evidence that long-term renal function is likely to be influenced to only a small extent by intervention for VUR comes the realization that the main reasons for treating the condition relate to quality of life – particularly the prevention of repeated upper UTIs, and avoidance of the need for repeat investigation procedures. Therefore, it becomes more difficult to justify open surgery and the associated risks, and the opinions of the parents/patients become more important. A survey of informed parental preference was published in 2003. The large majority of parents expressed a preference for endoscopic injection (80%), as opposed to antibiotic prophylaxis (5%) or open surgery (2%).

We anticipate continued advances in both equipment and techniques for endoscopic injection that will expand the indications of this treatment. For example, the most recent procedure, the HIT, has already proved successful in complicated cases, (e.g. double ureters, neurogenic bladder and Hutch diverticulum). Improvements in cure rate have also been demonstrated with the HIT, and it is adaptable to all grades of VUR. We therefore predict wider adoption of this method, allowing the endoscopic injection procedure to be standardised to a greater extent than at present. Refinements in the equipment used for the injection procedure (both the cystoscope and needle) have also raised the possibility of treating younger children, and investigations are ongoing to establish the feasibility of treatment during infancy. Injection with NASHA/Dx gel has recently been improved by introduction of a metal needle with markings to guide the depth of injection.

Our experience of using NASHA/Dx is that when patients are cured of VUR, they are highly unlikely to relapse during subsequent years. We generally perform a VCUG around 1 month post-treatment; if the result is negative, further VCUG investigations are only justified in case of pyelonephritis, as it may otherwise be assumed that reflux has been permanently cured.

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Conclusions

Advances during the last decade have significantly improved the outlook for children with VUR (Table 1). Few need now be subjected to open surgery as endoscopic treatment is established as an effective first-line treatment for VUR, with very few contraindications. Endoscopic injection is more compatible with the quality-of-life based rationale for treating the condition than more invasive surgery; parental preference also supports the use of endoscopic injection. Long-term antibiotic prophylaxis is increasingly considered as unfavourable, given the significant proportion of cases that do not resolve spontaneously, the occurrence of breakthrough infections and concerns about resistance.

As we move towards more widespread adoption of endoscopic injection, we look forward to the emergence of further clinical data to confirm the optimal approach to managing children with VUR.

References

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(TGF) reactivity, smooth muscle and mesangial cell proliferation and inhibits renin release. NO has been suggested to play a critical role in the development of different pathophysiological renal processes such as renovascular hypertension, renal inflammatory disease, pre-eclampsia and diabetic nephropathy. Less attention has been paid, however, to its role in obstructive nephropathy. NO has been shown to play a protective role in obstruction in preventing leukocyte migration and also in modulating the angiotensin II-induced vasoconstrictive response to ureteral ligation.

During complete obstruction, a marked reduction in RBF is found, and a redistribution of blood flow from outer to inner cortical layers takes place. In partial unilateral ureteral obstruction, there are indications of similar vasoactivity. Depending on the severity of the obstruction and the age of the individual at its onset, somewhat different results have been obtained.

The GFR is often found to be lower than would be expected from the RBF level. This seems to be the result of a reduction of the number of perfused glomeruli as well as changed filtration characteristics. Normally, the GFR is regulated by changes in the filtration pressure and the permeability of the glomerular membrane. The renal blood flow is autoregulated at a very constant level throughout a wide variety of diuretic conditions.

**Animal models**

Much of the experience derives from short or long term studies on the effects of total ureteral obstruction, and the effects on different parameters which are studied after different time intervals. Since total obstruction is very rare in the clinical situation, the effects of partial obstruction have also been studied in several models. Lewy and associates have used a strain of inbred Wistar rats with ureteropelvic junction obstruction and hydronephrosis. These kidneys have decreased GFR and increased arteriolar resistance. Chevalier has induced partial obstruction and hydronephrosis. These kidneys have decreased GFR and increased arteriolar resistance.

In the experimental studies at our own laboratory, rats have been submitted to partial ureteral obstruction at three weeks of age using the Ulm and Miller psoas groove technique. This model creates a considerable hydronephrosis with moderate functional impairment, which appears to be slightly progressive with time (Figure 2).

![Figure 2](Image)

**Filtration regulation; the tubuloglomerular feedback mechanism (TGF)**

The regulation of the glomerular filtration depends largely on the TGF mechanism, which acts as a negative feedback loop between the closely related distal tubule and the glomerular vessels. The macula densa cells respond to the increased salt content in the tubular fluid that follows increased filtration by reducing filtration pressure and thereby GFR normally by initiating afferent vasoconstriction. The TGF is of particular interest in this context as it has been shown in several studies from our own laboratory that the TGF properties are changed with obstruction.

The TGF mechanism is investigated by micropuncture approach using the stop-flow technique (Figure 3). Variations in the stop-flow pressure have been shown to accurately reflect concomitant changes in glomerular capillary pressure. The distal tubule is perfused at different rates with a modified Ringer solution. The sensitivity of the TGF response is characterized by the tubular flow rate at which 50% of the maximal drop in stop-flow pressure occurs (turning point) and the reactivity by the magnitude of the fall in stop-flow pressure at the highest perfusion rate used (DPsf).

**The filtration coefficient (Kf)**

The filtration coefficient (Kf) is an estimation of the filtering capacity, that is the available area and permeability of the filtering surface at a given moment. A reduction of the Kf as a part of the adaptation of the kidney to obstructive injury has been postulated by several investigators, being possibly mediated by one or several vasoactive substances, including NO. TxA2 has been shown capable of contracting mesangial cells in vitro, and NO increases Kf even at low concentrations. The aquaporin molecular structure of the glomerular membrane is now well described, and the porosity of the membrane is found to be highly variable.

**Investigations on partial obstruction and filtration regulation**

We performed micropuncture experiments and RBF measurements at different intervals between three weeks to one year after induction of partial obstruction. After three weeks, the baseline kidney function was only slightly affected. Kidney parenchymal weights, single nephron GFR and RBF were normal despite a significant hydronephrosis.

During volume expansion (VE), however, major changes occurred in the hydronephrotic kidney. The TGF sensitivity was reset to a much higher level and the mechanism was highly active. The Pd remained

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below baseline. As a result, the diuretic response was maintained low on the diseased side, which is the kind of response seen in normal kidneys at dehydration. These effects could be reversed by blocking either the thromboxane synthesis or receptor sites. Thromboxane blockade had no effect on RBF in any group, and nitric oxide blockade reduced the RBF to about half in all groups. During VE a significant RBF increase appeared in untreated experimental animals (mean +14%) in contrast to controls. After thromboxane or nitric oxide blockade, however, no renal blood flow increase could be seen in either group. In these series, efferent vasodilatation must also have been apparent because $P_a$ remained low.

Single nephron blood flow is higher in the hydronephrotic kidney since the number of perfused glomeruli is reduced. Nevertheless, the single nephron GFR (SNGFR) is about 10% lower than in controls. A reduction of the $K_f$ may be responsible for that. Despite a marked RBF increase during VE, which could itself act as a diuretic force, SNGFR was increased in hydronephrotic kidneys to only half the extent of that increase during VE, which could itself act as a diuretic force, SNGFR was increased in hydronephrotic kidneys to only half the extent of that increase during VE, which could itself act as a diuretic force, SNGFR was increased in hydronephrotic kidneys to only half the extent of that increase during VE, which could itself act as a diuretic force, SNGFR was increased in hydronephrotic kidneys to only half the extent of that increase during VE, which could itself act as a diuretic force, SNGFR was increased in hydronephrotic kidneys.

Blood pressure measurements

In recent experiments, the effects of unilateral hydronephrosis on arterial blood pressure were examined. Unilateral partial obstruction was created as described above. A month later, a telemetric blood pressure device was inserted and blood pressure recordings begun. Preliminary results indicate that the blood pressure is elevated in hydronephrotic animals in contrast to controls.

Concluding remarks

Defining the criteria which characterize obstruction have been attempted from many points of view, urodynamically as well as physiologically. At present there is no “gold standard” method which allows accurate assessment of obstruction. During the last ten years the management policy concerning asymptomatic hydronephrosis has become more and more conservative. In the absence of obvious signs of progressive kidney damage, these cases are managed nonoperatively. It has been shown that more than half of the kidneys improve with age, and “long-term” (3-5 years) follow-up shows that this can be done without a high risk for progressive renal damage. Besides the need for life-long follow-up with repeated investigations, other physiological side effects are basically unknown.

Much experimental research effort has been made to gain a further understanding of the mechanisms involved in obstructive kidney damage. Since the kidney is a paired organ, the functional adaptation to unilateral obstruction can serve to protect kidney function and parenchyma. This is an important pathophysiological process that seems to be very adequate from a renal point of view but may have certain long-term physiological costs. The contralateral kidney compensates for the reduction in total renal capacity by increased filtration and tubular reabsorption. The capability of this compensatory mechanism may be limited. The adaptational capacity of the hydronephrotic kidney to obstruction is definitely limited. A further understanding of the criteria that differ from irreversible changes from irreversible is important.

We have found that the functional adaptation of the kidney to partial unilateral obstruction includes a resetting of the TGF mechanism towards higher sensitivity and reactivity. This response is carried out at least partly by a thromboxane and/or nitric oxide dependent vasodilation that leads to a renal blood flow increase, which is proportional to the degree of obstruction; the greater the degree of hydronephrosis, the greater the blood flow increase. A reduction of the filtration coefficient also appears to be present in hydronephrotic kidneys. The net effect of these changes is that the response to fluid load is carried out mainly by the contralateral kidney, and the high, possibly damaging intrarenal pressures that may result from elevated diuresis in the hydronephrotic kidney, are avoided. One side effect is that these animals appear to become hypertensive. This phenomenon is further investigated in ongoing experimental as well as clinical studies.

References:

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17. Ulm A H, Miller F: An operation to produce experimental reversible hydronephrosis in dogs. J Urol 1962 88; 337-
Angiogenesis in Wilms’ Tumor and Neuroblastoma

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The pediatric urologist encounters a spectrum of retroperitoneal solid tumors in children. Of the kidney tumors, Wilms’ tumor (WT) is the most common and represents 90% of all kidney tumors. Other childhood kidney tumors comprise the benign congenital mesoblastic nephroma, the malignant rhabdoid tumor, and the clear cell sarcoma of the kidney. Of the non-renal retroperitoneal tumors, neuroblastoma (NB) is the most common, arising from the adrenal medulla, the sympathetic trunk, or paraganglia. NB can dislocate the kidney and also invade the kidney parenchyma. Both WT and NB are extensively vascularized, rapidly growing tumors that often present with metastases. In both cancers, surgical resection is necessary for cure, and surgical reduction of the tumor burden is beneficial also in advanced disease. WT and NB have, however, different prognoses; WT has an overall survival rate of ~ 88% 1, while NB has ~ 55%.2 Thus, there is a clinical need for new therapeutic strategies in cases of NB and WT with advanced disease. WT and NB have, however, different prognoses; WT has an overall survival rate of ~ 88% 1, while NB has ~ 55%.2 Thus, there is a clinical need for new therapeutic strategies in cases of NB and WT with poor prognosis, but eventually in all patients, in order to reduce the acute and late effects of chemotherapy in children.

Angiogenesis

Angiogenesis is new blood vessel formation by sprouting from pre-existing vessels. Angiogenesis is a tightly regulated physiological process, which is activated during placentation, embryogenesis, body growth, and wound healing. There is experimental and clinical evidence that angiogenesis is also a prerequisite for the growth and metastasis of solid tumors.3,4 Tumor angiogenesis is implicated in all steps of carcinogenesis: progression from a premalignant tumor to a malignant one, breakdown of the extracellular matrix and invasion of cells into the circulation, and growth of distant metastases. The more extensive the angiogenesis, the more rapid expansion of the viable tumor cell mass, and the more likelihood of metastasis (Figure 4). Angiogenesis is driven by angiogenic growth factors, secreted from or induced by tumor cells. The most well-known angiogenic growth factor is VEGF (vascular endothelial growth factor). The action of angiogenic growth factors is counteracted by endogenous inhibitors of angiogenesis (e.g. thrombospondin, angiostatin, endostatin). Hence, angiogenesis occurs if there is an imbalance between stimulators and inhibitors in favor of the former. This shift may be due to an excess of angiogenesis stimulators or loss of inhibitors. The complexity of the process is indicated by the fact that there are more than 20 known angiogenic growth factors and more than 15 endogenous inhibitors of angiogenesis. There are three clinical implications of angiogenesis in childhood retroperitoneal tumors: (1) prognostic tumor aggressiveness from microvascular counts in resected tumors, (2) monitoring efficacy of therapy by analyzing blood levels of angiogenic growth factors, and (3) treating with inhibitors of angiogenesis.

Recently, it was shown for the first time that a specific inhibitor of angiogenesis, bevacizumab (Avastin®; an anti-VEGF antibody) prolonged survival and delayed tumor progression in patients with metastatic colorectal cancer.5 There are over 30 inhibitors of angiogenesis in cancer clinical trials presently. Also, most chemotherapeutics inhibit endothelial cell migration and proliferation, and part of the anti-tumor effects seen with chemotherapeutics are likely mediated through inhibition of angiogenesis. Chemotherapy can target the untransformed vascular endothelium when given in a low dose frequently, i.e., metronomic scheduling.6 Specific inhibition of angiogenesis is considered to have less toxicity than chemotherapeutics given at the maximally tolerated dose.

What evidence do we have that WT and NB are angiogenesis dependent, and what indications do we have that angiogenesis inhibitors may become a complement to surgery, chemotherapy and radiotherapy in children with retroperitoneal tumors?

Angiogenesis in Wilms’ tumor

Angiogenesis, expressed as the highest microvascular density per field of view at X200 (the tumor “hot-spot”) in resected tumors was an independent prognostic marker in our series of 33 WT patients, in that vascular densities above the median had a poorer prognosis.7 The presence of tumor hot-spots probably reflects clones of tumor cells with high angiogenic potential, and it is possible that the tumor hot-spot represents the most aggressive part of the tumor (Figure 5). The hot-spot was
frequently found in the blastemal compartment. Angiogenic growth factors are present in tumor tissue from patients with WT, and serum levels of VEGF and HGF (hepatocyte growth factor, also an angiogenic growth factor) in children with WT were three times higher than in healthy controls. In fact, serum VEGF concentrations parallel the clinical course. In an experimental model for WT, anti-VEGF antibodies potentially reduced tumor growth. Also VEGF-trap, a high-affinity soluble decoy receptor for VEGF, reduced orthotopic WT growth in mice. The elevated serum levels of VEGF and expression of VEGF in tumor tissue found imply that VEGF inhibition may be considered for non-responding WT patients. Also, inhibition of HGF or its receptor c-MET may be a fruitful approach in WT.

Angiogenesis in neuroblastoma

Angiogenesis has been quantified in NB, and the vascular area correlated to metastatic disease and to a poor outcome, but data are conflicting. Serum and tissue levels of angiogenic growth factors and their receptors are elevated in patients with NB, both on protein and mRNA-levels. High levels of VEGF were seen in high-stage disease. Plasma and serum HGF, but not VEGF, correlated to outcome. In animal models, NB can be cured by injection of an endogenous inhibitor of angiogenesis, cleaved antithrombin III. Inhibition of VEGF signalling, both on the protein level and on the receptor level reduces the NB growth rate in mice. Currently, we are investigating the efficacy of angiostatic therapy in an orthotopic, metastatic model of human neuroblastoma in SCID (severe combined immunodeficiency) mice. (Figure 6).

Fig. 6 - Orthotopic neuroblastoma in a control mouse and in a mouse given metronomic scheduling of a chemotherapeutic for 10 days. Tumor (T), right kidney (RK), left kidney (LK). Note the presence of a normal adrenal gland above RK in Fig. 6b.

Conclusion

Angiogenesis is a prominent feature of Wilms’ tumor and neuroblastoma. There is clinical and experimental evidence that these retroperitoneal childhood cancers are angiogenesis dependent. Angiostatic therapy is a new treatment modality in cancer. Specific inhibition of angiogenesis may not be hampered by the dose-limiting toxicity or development of drug resistance associated with chemotherapy. Angiostatic therapy may become a valuable clinical tool, firstly by improving overall survival, and secondly by permitting a reduction of the accumulated chemotherapeutic dose without loss of tumor control.

References

Anticholinergic Treatment for Nocturnal Enuresis: Current Understanding and Future Expectations

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Introduction

Nocturnal enuresis (NE) is a multifactorial disorder resulting from three key pathogenic mechanisms: high arousal thresholds, excessive urine production at night, and reduced bladder volume or detrusor overactivity.1,2 Children with NE void smaller volumes than normal subjects3, and a small bladder is often an overactive bladder. Cystometric studies on children with NE, especially therapy-resistant cases, have shown that they may have frequent, uninhibited detrusor contractions during sleep, although the bladder may be stable during the day.4 Research at our centre indicates that enuretic children with polyuria and deficient arousal mechanisms respond favourably to antidiuretic treatment (desmopressin), whereas children with detrusor overactivity and deficient arousal mechanisms do not.1

Neural input to the detrusor is predominantly parasympathetic; the postganglionic cholinergic fibres extend through the pelvic nerves and produce excitatory effects in the bladder and inhibitory effects in the urethral sphincter.5 The parasympathetic branch of the autonomic nervous system is active during micturition, carrying voiding reflexes from the spinal cord, whereas the sympathetic branch facilitates urethral resistance during urine storage.5

Oxybutynin, the most extensively studied anticholinergic drug in urological practice, has both antimuscarinic and direct detrusor relaxant properties. The drug exhibits similar pharmacokinetics in children and adults.6

Oxybutynin has proven effective in urge incontinence and in the overactive neuropathic bladder.7 The rationale for its use in nocturnal enuresis is based on the assumption that detrusor overactivity contributes to the pathogenesis of this disorder as well. However, despite a good tolerability profile in adults and children6, the doses required for a positive outcome in enuresis may produce side effects.6,8 Atropine-like adverse events, a result of its parasympatholytic properties, represent 49% of the total.9

This review assesses the efficacy of oxybutynin alone and in combination with desmopressin for the treatment of enuresis and determines which subgroup of children that may benefit from treatment. The efficacy of a new antimuscarinic drug, tolterodine, has recently been shown to be similar to oxybutynin in adults, while side-effects were less common. Preliminary data also indicate that this may be the case in the paediatric population as well10, but the drug has yet not been tested in NE. It is likely that the conclusions that are drawn below regarding oxybutynin will in the future prove true for tolterodine.

Efficacy of oxybutynin in enuresis

Few studies have assessed the efficacy of oxybutynin in the treatment of enuresis (Table 2). Many of them used weak methodologies with no randomization, no placebo, poorly defined or mixed patient populations of children with both enuresis and daytime incontinence. The studies by Buttarazzi and by Luque Arana unfortunately used poor inclusion criteria that the positive conclusions reached cannot be supported.11,12 Persson-Jünemann et al.13 administered oxybutynin 5-15 mg to a 63 of...

Table 2 -Studies of Oxybutynin Treatment in Nocturnal Enuresis

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Study design*</th>
<th>Children with daytime symptoms included?</th>
<th>Results</th>
<th>Comments</th>
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<tr>
<td>Thompson -76</td>
<td>30</td>
<td>RP</td>
<td>Yes</td>
<td>77% responded</td>
<td>Increased bladder capacity following oxybutynin 5 mg</td>
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<tr>
<td>Buttarazzi -77</td>
<td>39</td>
<td>OU</td>
<td>Yes</td>
<td>41% responded</td>
<td>Poor inclusion criteria</td>
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<tr>
<td>Persson-Jünemann -93</td>
<td>63</td>
<td>OU</td>
<td>Yes</td>
<td>70% responded</td>
<td>Responders had low bladder capacity</td>
</tr>
<tr>
<td>Luque Arana -89</td>
<td>15</td>
<td>OU</td>
<td>Yes</td>
<td>75% responded</td>
<td>All children included had detrusor overactivity</td>
</tr>
<tr>
<td>Kosar -99</td>
<td>36</td>
<td>OU</td>
<td>Yes</td>
<td>47% responded</td>
<td>All children with detrusor overactivity responded</td>
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<td>Marconi -85</td>
<td>58</td>
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<td>Yes?</td>
<td>86% responded</td>
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<td>Varan -96</td>
<td>9</td>
<td>Comp</td>
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<td>no significant effect</td>
<td>------</td>
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<td>RP</td>
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<td>------</td>
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<tr>
<td>Laurenti -87</td>
<td>50</td>
<td>OU</td>
<td>Yes</td>
<td>75% responded</td>
<td>Combination oxybutynin + imipramine given</td>
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<td>Caione -97</td>
<td>48</td>
<td>OU</td>
<td>Yes, exclusively</td>
<td>54% responded</td>
<td>71% responded to combination oxybutynin + desmopressin</td>
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<tr>
<td>De Grazia -99</td>
<td>89</td>
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<td>Yes, exclusively</td>
<td>93% responded</td>
<td>6 months treatment</td>
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<td>Nevéus -99</td>
<td>33</td>
<td>OU</td>
<td>No</td>
<td>61% responded</td>
<td>Combination oxybutynin + desmopressin given</td>
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* OU = open, uncontrolled; Comp = comparison with other drugs; RP = randomized, placebo-controlled

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with antidiuretic treatment was tested. A total of 48 patients with enuresis, with oxybutynin 5 mg tid or dicyclomine 20 mg t.i.d. Eighty-nine percent of children taking oxybutynin had a >60% reduction in wet nights compared with only 14% of children taking the other drug. Varan et al. investigated the efficacy of oxybutynin, pseudoephedrine or indomethacin in enuretic children. Oxybutynin did not significantly reduce the number of wet nights, but the number of children included was small (n=29), given the number of treatments given. Thompson and Lauvetz performed a double-blind, placebo-controlled cross-over study on children with cystometrically documented uninhibited detrusor activity. There was marked improvement of symptoms, including enuresis, with oxybutynin 5 mg bid. However, the study did not clearly define patient numbers or their disease status.

Lovering et al. performed the only double-blind, thus far, placebo-controlled study assessing the efficacy of oxybutynin in children with NE without concomitant daytime incontinence. Thirty children were given oxybutynin (10 mg per day) at suppertime over a 4-week period, followed by placebo for 4 weeks. The results showed no significant difference in the number of dry nights (p=0.181). Laurenti et al. treated 50 children, 12 of whom had concomitant day-time symptoms, with oxybutynin (5 mg bid) and imipramine for one month. In total, 37 (74%) patients responded with a >90% reduction and 9 (18%) with a 60-90% reduction in wet nights. Many patients were, however, lost to follow-up, which may indicate low tolerance with the treatment.

In an Italian multicentre trial, oxybutynin alone and in combination with antidiuretic treatment was tested. A total of 48 patients with enuresis and daytime incontinence or urgency were assigned to desmopressin (30 ug per day intranasally) plus oxybutynin (0.2 mg/kg bid) or oxybutynin alone. The results showed that the combination was more effective than oxybutynin alone (71% vs 54%). The results are still not very remarkable, since three or fewer wet nights per week was defined as a good clinical response. No cross-over design was used, nor was a placebo. In a Spanish study, 89 children with enuresis, daytime incontinence and urgency were treated with desmopressin (20 ug per day intranasally) and oxybutynin (5-15 mg daily) for six months. Fifty-five children were followed for one year. After 3 months of treatment, daytime disturbances were no longer present and 87 patients were completely dry after 6 months. Treatment was discontinued at 4 months and no anticholinergic side effects were reported. Although these results are impressive, the sample was not homogenous with 74% of children having associated daytime wetting. Furthermore, after one year almost 50% of patients had dropped out and were not included in the analysis.

The potential of combination therapy was tested at our center in an open pilot study of oxybutynin (5 mg bid) plus desmopressin (0.4 mg at bedtime) in a homogenous group of children with desmopressin-resistant NE. Overall, 20/28 (71%) children had at least a 50% reduction in wetting frequency and 13 children became completely dry.

**Tolerability of anticholinergics in enuresis**

Side effects are often reported from patients receiving oxybutynin, and although the majority are minor, they account for withdrawal in up to 27% of patients. There is also an important and often neglected risk of the accumulation of residual urine.

Dry mouth is experienced in many patients; visual disturbances and dizziness are more common in the elderly, whereas psychiatric disturbances (agitation, aggressivity, nightmares) may be more common among children. Kosar et al. found that 12% of children taking oxybutynin experienced constipation. This is a particularly bothersome side effect, since many of these children are constipated from the start, and the accumulation of faeces in the rectum may in itself cause detrusor overactivity.

**Predictors of response to parasympatholytic treatment in enuresis**

Enuresis comprises several aetiological factors and not all patients will respond to the same treatments. Oxybutynin can be suspected to be most effective in enuretic patients with detrusor overactivity and accordingly decreased voided volumes. The above-mentioned studies by

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Persson-Jünemann and Kosar clearly indicated that cystometrically proven detrusor overactivity was prognostic of a good therapeutic response, regardless of daytime symptoms. A recent study by our research group sought to define the pre-treatment characteristics of patients who would benefit from anticholinergic treatment. Children included had primary NE for at least 6 out of 14 nights. Renal concentrating capacity and bladder parameters were compared between 27 desmopressin responders, 11 oxybutynin responders, 7 responders to desmopressin and oxybutynin combined, 23 therapy-resistant children and 55 dry controls. The characteristics of different treatment-responder types are shown in Table 3. The results confirm that oxybutynin responders generally have small bladders, whereas children responding to desmopressin or to combination treatment were most likely to be polyuric.

Conclusion

Oxybutynin is not supported by evidence-based therapy in NE. The use of the drug in children with NE is based on theoretic considerations and translation from studies in adults. There are, as yet, no studies of parasympatholytics in children with NE and/or daytime incontinence that fulfill regulatory requirements. A lack of dose-finding studies in children also weakens their use.

Still the use oxybutynin, or the combined use of antidiuretic therapy and oxybutynin, has shown benefit in some patients with NE. The children most likely to respond are those non-responsive to standard first-line therapy, children with signs of detrusor overactivity, children with concomitant daytime symptoms (incontinence or urgency) or small voided volumes. Children without these characteristics are unlikely to benefit.

Before the treatment potential and suitability of oxybutynin, or other anticholinergics such as tolterodine, can be fully assessed, there is need for extensive research. Research considerations should be focused on randomized, placebo-controlled studies of children with therapy-resistant enuresis. Studies of unselected patient groups are neither relevant nor of benefit to the bedwetting children.

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