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van Ophoven A[1], Hertle L[1]
1. Dept. of Urology, University Hospital

SAFETY AND EFFICACY OF AMITRIPTYLINE FOR THE TREATMENT OF INTERSTITIAL CYSTITIS: RESULTS OF A PLACEBO CONTROLLED TRIAL AND A PROSPECTIVE LONG TERM OBSERVATIONAL STUDY.

Hypothesis / aims of study
Interstitial cystitis (IC) is a debilitating bladder syndrome, primarily affecting women. Despite a large number of purported therapeutic approaches [1] the treatment of IC remains suboptimal and the data regarding the efficacy of the majority of those treatment modalities derived primarily from non evidence based trials [2]. The efficacy of AMI has never been assessed in a randomized, placebo-controlled, double-blind study until now. We additionally conducted a prospective open-label study to examine the safety and efficacy of long term administration.

Study design, materials and methods
The randomized controlled study comprised 50 patients (44 women, 6 men) who all met the diagnostic criteria of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) for IC. The patients were randomly assigned to AMI or placebo. Patients were prospectively treated for 4 months with a self-titration protocol that allowed escalation of drug dosage in 25mg increments in 1 week-intervals (maximum dosage 100mg). The change from baseline in the IC symptom and problem score (O´Leary et al) was the primary outcome parameter for this study. The long term study enrolled 94 IC patients (82 women, 12 men) of whom 59 (63%) met the diagnostic criteria of the NIDDK for IC. The drug was again taken strictly at bedtime following the aforementioned self-titration protocol without a limitation of the maximum daily dosage. Patients reporting improvement of symptoms on a 7-point centered scale were defined as treatment responders (primary outcome). Finally, patients were requested to rate their overall satisfaction with the therapeutic outcome. Changes in functional bladder capacity and frequency (48-hours voiding log) and intensity of pain and urgency (visual analog scales) were chosen as secondary outcome parameters in both trials.

Results
2 patients (1 AMI, 1 placebo patient) dropped out of the controlled study due to side effects. The mean symptom score decreased from 26.9 to 18.5 in the amitriptylin group compared with 27.6 to 24.1 in the placebo group ($p = 0.005$). Of the patients in the AMI group, 42% had a greater than 30% decrease in the symptom score compared with 13% in the placebo group ($p < 0.001$). Both pain and urgency intensity improved statistically significant in the AMI group compared with the placebo group ($p < 0.001$). The frequency and functional bladder capacity improved to a much greater degree in the AMI group, but the differences were statistically not significant ($p = 0.06$, $p = 0.08$). Anticholinergic side effects were noted by all except 2 patients in the AMI group (92%) and by 5 patients in the placebo group (21%). The mean follow up in the observational study was 19 months and the mean treatment duration was 16 months. Response to treatment was observed in 60 patients (64%). Overall mean dosage was 55mg (range 12.5 – 150mg). Anticholinergic side effects occurred in 79 patients (84%) (dry mouth: 79%, weight gain: 59%). Patient overall satisfaction with the therapeutic result was either excellent or good in 43 patients (46%) (excellent satisfaction: 15%, good: 31%). The drop-out rate was 31% (29 patients) after a mean treatment period of 6 weeks at a mean dosage of 70mg. Non-response to treatment was the primary reason for drop-out in all cases, side effects contributed to drop-out in 25 patients (86% of all drop-outs). The following symptoms improved statistically significant compared with baseline: Pain intensity (-22.1mm. on visual analogue scale, $p=0.002$), urgency (-19.7mm., $p=0.004$), 24-hr frequency (-6.9 voids/d, $p=0.021$), functional bladder volume (+32.9ml, $p=0.039$). The O´Leary/Sant score dropped by 7.9 points under treatment ($p=0.004$). Response rates and extent of symptom improvement did not differ significantly between the patients fulfilling NIDDK criteria and those with the “clinical diagnosis” of IC.

Interpretation of results
In both trials treatment with amitriptyline significantly improved the primary and most of the secondary outcome parameters in patients suffering from IC. Adverse events, although mostly mild and similar to those in previous reports constitute the major drawback of this

therapeutic approach to IC. The therapeutic long-term response to amitriptyline was uniformly observed in patients fulfilling the NIDDK criteria and in those patients with the pure clinical diagnosis of IC.

Concluding message

Long term AMI therapy is feasible, safe and effective for treating IC. Anticholinergic side effects are a key co-factor for treatment termination and constitute the major drawback of AMI treatment. Low starting doses and careful dosage titration including strict administration at bedtime may help to manage the side effects

1. Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. Urology 56(6), 940-5. 2000.

2. Pitfalls in the design of clinical trials for interstitial cystitis. Urology 60(5), 742-8. 2002.