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Use of Desipramine for the Treatment of Overactive Bladder Refractory to Antimuscarinic Therapy

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Purpose: To evaluate the use of desipramine in the treatment of overactive bladder (OAB).

Materials and Methods: We retrospectively evaluated 43 patients who were treated with desipramine for OAB refractory to antimuscarinic therapy. These OAB patients were stratified by the presence or absence of bladder pain.

Results: Forty-three patients were evaluated with a mean follow up time of 12.2 ± 4.6 months. The mean age of the patients was 71 ± 16 years. Twelve patients (28%) discontinued desipramine, 9 due to perceived lack of efficacy, 2 due to central anticholinergic side effects, and 1 due to the development of oropharyngeal sores. Patients were stratified into two subgroups based upon treatment with desipramine for OAB alone ($n = 29$) or OAB and bladder pain ($n = 14$). There was no difference between the groups in regard to sex ($P = .34$), prior history of radiation ($P = .19$), side effects ($P = .16$), and specifically evaluated central anti-cholinergic side effects ($P = .66$). There was no statistical difference in the self-reported success rate of the medication ($P = .48$). In the OAB plus bladder pain subgroup, 71% of patients reported improvement in their pain. Overall, 13 (30%) patients had history of prior pelvic radiation and 10 of those (77%) reported improvement with desipramine.

Conclusion: Desipramine is a potential useful treatment for patients with OAB. In addition, it can be used in patients with OAB and bladder pain and patients with complex OAB such as OAB caused by pelvic radiation.

Keywords: urinary incontinence, urge; cholinergic antagonists; drug therapy; antidepressive agents, tricyclic; treatment outcome.

INTRODUCTION

Overactive bladder (OAB) is a condition characterized by increased urinary urgency, with or without incontinence.⁽¹⁾ Its prevalence has been estimated to range between 11.8% and 14%, slightly lower in men than in women.^(2,3) This symptom profile has been shown in several studies to increase with age.^(2,4,5) The incidence increases from 10.5% for patients aged 18-24, up to 21.9% for those aged greater than 65 years.⁽³⁾ In elderly patients who fail conservative treatments for OAB, pharmacologic management can be challenging.⁽⁶⁾ Traditionally, anticholinergic agents such as oxybutynin are used as a first-line pharmacologic treatment.⁽⁷⁾ If the patient symptoms are refractory to treatment with traditional first-line anticholinergic agents, tricyclic antidepressants (TCAs) such as amitriptyline and imipramine can be prescribed. However, a limitation of all anticholinergic agents on the market is their lack of specificity for muscarinic receptors of the bladder. As a result, central anticholinergic side-effects including memory defects, fatigue, and impaired balance can often be experienced.⁽⁶⁾ Furthermore; elderly patients are particularly vulnerable to these side-effects associated with the central anticholinergic effects of TCAs. This is due in part to an increased anticholinergic load, polypharmacy, a natural age-related decline in cholinergic function, and declining function of the blood brain barrier.⁽⁶⁾

Desipramine is an active metabolite of imipramine. It is distinguished by the presence of only one n-methyl group on its side chain.⁽⁷⁾ It has been shown in several studies to have less central nervous system (CNS) side effects than other TCA agents including imipramine and amitriptyline.⁽⁷⁻⁹⁾ No published study has evaluated the use of desipramine as a treatment for OAB. Herein, we report on our experience with desipramine for the primary treatment of symptomatic OAB with the goal of minimizing CNS-related side-effects.

MATERIALS AND METHODS

Data Collection

Data was prospectively collected on patients that were prescribed desipramine by a single physician (GHW) for the second-line treatment of OAB over a two year period spanning between 2010 and 2011. Diagnosis of OAB was based

upon established AUA guidelines.⁽¹⁰⁾ Patients were informed about the off-label use of desipramine for this purpose. An inclusion criterion was OAB refractory to prior anticholinergic treatment. Patient demographics, clinical characteristics, and patient-reported outcomes, and side-effect profiles while taking desipramine were retrospectively reviewed. Patients were followed serially at monthly visits to assess the therapeutic effects as well as side effects of the medication regimen. Data collection and analysis for this study was approved by the Institutional Review Board (IRB) and all patient data was stored in a secure patient de-identified database in accordance with the IRB approval.

Statistical Analyses

All statistical analyses were conducted on Microsoft Excel 2007 platform. Continuous and categorical variables were analyzed using Mann-Whitney *U* test and Chi-Squared test, respectively.

RESULTS

Forty-three patients were evaluated who were prescribed desipramine after failing treatment with at least one antimuscarinic agent. Failure from an antimuscarinic agent was determined through chart review. The initial dosing of all patients was 10 mg. The range of final dosing was 10 mg to 75 mg. Two patients (5%) dosages were raised to 25 mg, 3 (7%) to 50 mg and 1 (2%) to 75 mg. Their dosages were raised based on clinical evaluation of patient self-reported symptom benefit and side effects. The mean age of the patients was 71 ± 16 years (Table 1). Twenty-three patients (53%) were male and 20 (47%) were female. Overall, 13 (30%) patients had history of prior pelvic radiation and 10 of those (77%) reported improvement with desipramine. Thirty-one (72%) of the original 43 patients continue to take desipramine as prescribed at a mean follow up of 12.2 ± 4.6 months, reporting clinical benefit and improvement of their OAB symptoms. Twelve patients (28%) discontinued desipramine, 9 (75%) due to perceived lack of efficacy, 2 (17%) due to central anticholinergic side effects, and 1 (8%) due to the development of oropharyngeal sores. The average duration of compliant use of the medication in these patients who discontinued use was calculated at 6 ± 3.4 months. Overall, 12 patients

Table 1. Baseline characteristics of patients prescribed desipramine for overactive bladder.

	Patients
Number	43
Male	23
Female	20
Age ± SD, years	71 ± 16
Side effects, n (%)	12 (28)
Central anticholinergic side effects, n (%)	7 (16)
Prior pelvic radiation, n (%)	13 (30)
Patients doing well on medication, n (%)	31 (72)

Key: SD, standard deviation.

reported side effects from the medication, the most common being dry mouth (n = 5, 42%), constipation (n = 2, 17%), and fatigue (n = 3, 25%).

Furthermore, patients were stratified into two subgroups based upon desipramine treatment for OAB alone (n = 29) or OAB combined with bladder pain (n = 14) (Table 2). There was no difference noted between the groups in regard to sex ($P = .34$), prior history of pelvic radiation ($P = .19$), side effects ($P = .16$), and specifically assessed central anticholinergic side effects ($P = .66$). However, the OAB plus bladder pain group was significantly older ($P = .05$). There was no statistical difference in the self-reported success rate of the medication ($P = .48$). In the OAB plus bladder pain group 10 (71%) patients reported improvement in their pain in addition to OAB symptoms.

DISCUSSION

CNS side effects from treatment with anti-muscarinic agents include headache, fatigue, dizziness, cognitive impairment, confusion, and insomnia.⁽¹¹⁾ TCAs have similar side-effects due to their adjunct anticholinergic properties.⁽¹¹⁻¹³⁾ More elderly patients are more likely to suffer from OAB and are also more likely to experience anticholinergic side-effects from the medications used to treat their symptoms.⁽¹²⁾ This increased risk is commonly attributed, at least in part, to polypharmacy which is more prevalent in this population with more comorbidity. Gardner and colleagues estimated that between 21% and 32% of nursing home residents are

Table 2. Comparison of patients prescribed desipramine for overactive bladder only and for overactive bladder plus bladder pain.

	OAB Only	OAB and Bladder Pain	P
Number	29	14	-
Male	18	5	.19
Female	11	9	
Age ± SD, years	68.4 ± 18.0	76.7 ± 8.5	.05
Side effects, n (%)	6 (21%)	6 (43)	.16
Central anticholinergic side effects, n (%)	4 (14)	3 (21)	.66
With prior pelvic radiation, n (%)	9 (31.0)	4 (28.6)	.34
Patients doing well on medication, n (%)	22 (75.8)	9 (64.3)	.48

Key: SD, standard deviation; OAB, overactive bladder.

simultaneously prescribed two or more medications with anticholinergic activity.^(3,13) In addition, the elderly may have diminished efficiency of drug metabolism and elimination, leading to an increased anticholinergic “load” effectively.⁽¹⁴⁾ Delirium can be caused by blockage of brain muscarinic receptors and drugs with anticholinergic activity are the most common cause of drug-induced delirium.^(15,16)

Among the TCA agents, desipramine has been noted to have the least anticholinergic affect.⁽¹⁵⁾ In initial clinical trials, it was noted to have less CNS side effects when compared to imipramine.⁽⁹⁾ These findings were corroborated in two subsequent studies.^(7,11) A randomized control trial of 20 patients comparing imipramine and desipramine use for the treatment of major depression, found that although desipramine was not superior to imipramine in its treatment of depression symptoms, it is less likely to produce central anticholinergic side effects such as headache, tremors, and dizziness.⁽¹⁰⁾ Di Mascio and colleagues enrolled 7 blinded subjects who were given either a dose of imipramine (50 mg, 100 mg or 200 mg) desipramine (50 mg, 100 mg, and 200 mg) or a placebo. Subjects were then tested performing various cognitive and visuo-motor tasks such as typing, aiming and performing calculations. They found that imipramine produced marked impairment in intellectual and visuo-motor function in comparison to desipramine.⁽⁷⁾

Desipramine has also been compared to amitriptyline in head-to-head investigation. In a double blinded crossover study by Blackwell and colleagues, nine healthy female volunteers

were given three different doses of desipramine (25 mg, 50 mg, and 100 mg), three different doses of amitriptyline (25 mg, 50 mg, and 100 mg) and placebo. The patients then were asked to rate their sedation on Clyde Mood Scale. Amitriptyline was noted to produce more sedation at all levels and was clinically significant at 50 mg ($P < .01$).⁽⁸⁾ In a study of pigeons by Vaillant, the central anticholinergic effects of desipramine, amitriptyline and imipramine were assessed by measuring their ability to mask the central muscarinic effects of physostigmine.⁽¹⁷⁾ Desipramine was found to be the least effective in CNS function of the TCAs tested, requiring the highest dose to reverse the central muscarinic activity of physostigmine. Furthermore, in a study by Abernethy and colleagues, metabolic clearance of desipramine was found to be less affected by increasing age than that of imipramine.⁽¹⁸⁾ In consideration of its decreased central anticholinergic activity, we sought to report on the use of desipramine for patients with OAB refractory to treatment with first-line antimuscarinic agents. To our knowledge this is the first study reporting on the use of desipramine for OAB. Our results indicate that it is well tolerated in a population of patient's refractory to antimuscarinic therapy. Also significant was that 77% of patients with prior history of pelvic radiation reported improved symptoms following desipramine treatment, as this population can be difficult to treat.⁽²¹⁾ Furthermore, only two patients discontinued the medication due to central anticholinergic side-effects and the vast majority (72%) reported improvement on the prescribed therapy with desipramine. Patients with bladder pain and OAB can be difficult to manage, since many of them can fall into the Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) spectrum.⁽¹⁹⁾ For IC/BPS patients' amitriptyline has been the most extensively TCA agent studied. In a large double blinded randomized control trial by Foster and colleagues comparing behavior modification and education with and without amitriptyline, they found that patients who could tolerate a low dosing (25 mg) had significant benefit from the drug.⁽²⁰⁾ Desipramine has also been studied in the setting of IC/PBS. Renshaw reported on the successful use of desipramine in a single patient.⁽²¹⁾ In our study we reported 71% of patients subjectively reported an improvement in their bladder pain. Our study is limited by its retrospective nature and single-

arm design which cannot fully access the comparative efficacy of desipramine as a single-agent treatment modality for OAB. Future, prospective randomized studies are needed on this topic to fully elucidate the utility and side-effect profile of desipramine over other agents as a treatment option for OAB.

CONCLUSION

Our experience to date has demonstrated desipramine as a useful potential treatment for patients with OAB refractory to first-line antimuscarinic therapy, possibly providing an alternative treatment modality with a mechanistically minimized risk of CNS side-effects compared to other TCAs.

CONFLICT OF INTEREST

None declared.

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