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Research paper

Calcium channel blocker associated lower urinary tract symptoms in males: an Australian retrospective observational study

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ABSTRACT

Background Lower urinary tract symptoms (LUTS) are common and prevalence increases with age. In men, voiding symptoms are more commonly encountered than storage symptoms. LUTS are often associated with chronic diseases but their pathophysiology requires further study. We aimed to determine whether calcium channel blockers (CCBs) worsened, improved or did not alter symptoms of urinary obstruction in males aged 45 years and above with medical conditions associated with urinary obstruction.

Methods A cohort retrospective observational study was undertaken to identify the effect of the use of CCBs on LUTS in males over 45 years of age. Participants were recruited from four community pharmacies and a general practitioner surgery. Eligible participants provided informed consent and were administered a standardised questionnaire (IPSS) to obtain information on LUTS and quality of life (QOL) prior to and after commencement of CCB therapy.

Results Thirty-eight males were enrolled in the study, and their ages of ranged from 46.2 to 88.7 years, with the mean age being 66.9 years (95% CI: 63.9–69.9). The mean IPPS score prior to commencing a CCB was 3.13 (95% CI: 2.09–4.17) compared to 9.82 (95% CI: 7.83–11.80) whilst on the drug ($P<0.001$). After adjusting for other medications and conditions which may contribute to LUTS, and for the natural progression of LUTS with ageing, the change remained significant. The increase in IPPS score was associated with a significant decline in the respondents' QOL.

Conclusion The results of this study suggest that in middle-aged males the introduction of a CCB may be associated with worsening of LUTS, and an associated decline in QOL, although this will need to be confirmed in large prospective studies. However, given the common use of these agents in males to treat a range of cardiovascular conditions, we would suggest that men prescribed a CCB should be questioned about urinary symptoms before and after commencing treatment.

Keywords: benign prostatic hyperplasia, calcium channel blockers, lower urinary tract symptoms, male, quality of life

How this fits with quality in primary care

What do we know?
Lower urinary tract symptoms (LUTS) are common in both males and females, and the prevalence increases with age. In contrast to females, voiding symptoms are more commonly encountered than storage symptoms in males. LUTS are often associated with chronic diseases, however, their pathophysiology requires further study.

What does this paper add?
This study provides evidence of a possible association between the use of CCBs and the worsening of LUTS in males. As CCBs are amongst the most widely prescribed drugs in the world, and patients with LUTS often do not seek treatment, it is recommended that males commenced on one of these agents should be questioned about the development of LUTS, and in those with established LUTS alternative agents be considered.

Introduction

The term 'lower urinary tract symptoms' (LUTS) encompasses three groups of symptoms which include problems with voiding (slow stream, intermittency, hesitancy, straining), post-micturition (sensation of incomplete emptying, post-micturition dribbling) and urine storage (frequency, urgency, nocturia).[1,2] LUTS in men can occur as a result of several factors, including benign prostatic hyperplasia (BPH), systemic illnesses, surgical procedures and medications.[3] BPH is the most common underlying aetiological factor in men with LUTS, and it can interfere with normal voiding. Fifty percent of men aged over 50 years will develop microscopic BPH, of whom half will develop LUTS.[3]

Urinary obstruction may be worsened by inhibition of the contractile processes; and storage (irritative) symptoms may be improved by inhibition of the contractile processes. The two main functions of the lower urinary tract, to store urine without leakage for a long period of time and to rapidly expel it during micturition, occur naturally in normal life.[1,2] These processes involve a very complex interaction between the structural or anatomic parts of the urinary tract and the peripheral and central nervous systems. To respond to the nervous and hormonal control systems, each part of the urinary tract muscles has specific receptors for the transmitters, released from nerves or generated locally, and the associated cellular pathways for initiating contraction and relaxation.[1] In addition to these demands on integrative control, both filling and emptying of the urinary bladder provide a challenge to the muscle components in the walls of the lower urinary tract.[1]

In men with BPH, the bulk of the enlarged prostrate can become obstructive, which is known as mechanical obstruction.[4] Up to 50% of patients with BPH-induced obstruction may also have involuntary bladder contractions, due to detrusor muscle instability.[5] The storage symptoms of BPH and urge incontinence have been positively correlated to detrusor muscle instability.[4] These are reported to occur in between 50% and 80% of men with bladder outlet obstruction due to BPH.[3]

It has been shown that alterations in muscle tone, which may accompany bladder outlet obstruction, have significant effects on bladder capacity and compliance.[6] In the initial phases of outflow obstruction, there is transient decompensation of the bladder smooth muscle, which initiates the molecular events that lead to hypertrophy of the smooth muscle and a compensatory increase in detrusor pressure to maintain urine flow in the face of increased outflow resistance.[7] Prolonged partial bladder outflow obstruction is accompanied by a progressive decrease in contractility of detrusor smooth muscle,[8] which is likely to be accompanied by breakdown of the structure and function of the proteins that enable the smooth muscle cells to take up, store, and release calcium (Ca^{2+}), affecting the calcium activation of the contractile apparatus.[9,10]

The calcium channel subtype present in detrusor smooth muscle is the L-type voltage dependent channel and it has a major role in muscarinic receptor facilitation of acetylcholine and noradrenaline release.[11,12] Normal physiological voiding, as well as generation of abnormal bladder contractions in diseased states, is critically dependent on acethylcholine-induced stimulation of contractile muscarinic receptors on the smooth muscle of the urinary bladder.[13] Outflow obstruction induces stability affecting changes in muscarinic and adrenergic receptor functions, and in non-adrenergic-non-cholingeric (NANC) mechanisms relevant for detrusor contraction and relaxation.[4] NANC-mediated contraction may be a greater contributor to the contractile process in detrusor instability,[5] and adrenergic (via α-adrenoceptors)-mediated mechanisms may play a more significant role in contractile function in the obstructed bladder.[14]

It has been suggested that overactivity of the detrusor muscle due to BPH may be induced by hyperpermeability of smooth muscle cell membrane to calcium.[15] Animal studies have shown the potential of CCBs to reduce bladder overactivity and increase bladder capacity.[9,16,17] Although experimental data provide a theoretical basis for the use of CCBs in the treatment of detrusor overactivity in humans, there have been few clinical studies focusing on the ability of CCBs to reduce the irritative symptoms in humans with overactive detrusor muscle, and these few studies have produced mixed results.[18–22]

Findings of prior research have also demonstrated that antagonism of Ca^{2+} channels in detrusor muscles inhibits urinary bladder contraction,[17,23,24] increases the time taken to reach maximal bladder pressure, reduces maximal power of contraction, decreases maximal rate of emptying[25] and reduces bladder filling rates which may subsequently cause polyuria, micturition frequency, micturition disorder and nocturia.[26] CCBs appear to significantly affect the contractile process, particularly in the obstructed bladder. These agents also reduce the urethral muscle tone and induce natriuresis.[27,28] These processes may place the subset of males with urinary obstruction at an increased risk of experiencing LUTS. This study was therefore undertaken to determine the effect of CCB use on LUTS in males over the age of 45 years who may have medical conditions associated with urinary obstruction.

Methods

This retrospective observational study used patients as their own controls. The study targeted males aged 45 years and above currently taking or presenting with a repeat prescription for a CCB. Following ethics approval, patient recruitment was undertaken at community pharmacies and a medical practice in the south-west suburbs of Perth, Western Australia from July 2002 to May 2005. General practitioners (GPs) and pharmacists were asked to identify and invite patients to participate in the study. Patients were given an information sheet which explained the purpose of the study and what actions they would be required to undertake if they agreed to take part in the study.

Patients who agreed to participate in the study were asked to sign a consent form, in which they also entered their contact details and their doctor's contact details, and agreed to their GPs being contacted regarding their medications and/or medical conditions, and whether they had just commenced or were on chronic CCB therapy. Each consent form was forwarded to the primary investigator and the information was added to a secure database and assigned a unique patient identification code.

Patients were contacted by the primary investigator to arrange a suitable time to administer the International Prostate Symptom Score (IPSS)[29,30] questionnaire to assess each participant's LUTS, with increasing scores indicating more severe symptoms. The IPSS questionnaire addresses symptoms such as incomplete emptying, frequency, hesitancy, urgency, weak stream, straining to initiate urination and nocturia. The symptom scale of the IPSS has been reported to be a reliable measure; in a prospective revalidation of the instrument, the internal consistency reliability statistic, Cronbach α, was 0.86, and the one-week test–retest correlation was 0.92. Given the absence of a gold standard for self-perceived lower urinary tract symptom severity in men with histological BPH, the construct validity of the instrument has been assessed in many experiments.[31] The IPSS was originally designed for self-administration to eliminate potential interviewer bias, but studies have shown that an interviewer asking the questions and obtaining responses without 'coaching' gets similar answers.[32–35]

The American Urological Association (AUA) symptom index[36] is identical to the IPSS questionnaire, and references pertaining to either the AUA symptom index[31] or the IPSS questionnaire were considered to be equally applicable to both. Based on the correlation between IPSS scores and patients' ratings of bother of their condition, the symptom scores were categorised as 'mild' (0 to 7 points), 'moderate' (8 to 19 points) and 'severe' (20 to 35 points). The only real clinical usefulness of these groupings is that men with mild symptoms are rarely bothered enough to desire treatment.

The AUA Benign Prostatic Hyperplasia (BPH) Impact Index[37] combined with a global IPSS impact question was used in a questionnaire administered by interview to assess the impact of LUTS on the patients' quality of life (QOL). Each participant was asked to answer both questionnaires twice, based on symptoms and QOL prior to and after commencement of CCB therapy. The total scores ranged from a minimum of zero, indicating no adverse impact on QOL, to a maximum of 19, indicating maximal adverse impact on QOL. Patients were also asked to complete a symptom diary for 31 days, the seven symptoms measured in the diary matching the validated seven-symptom IPSS questionnaire. The symptom diary score was then compared to the patients' second IPSS questionnaire responses, which related to their LUTS after commencement of their CCB: the correlation between the two was used to validate the patients' recall ability.

Natural progression of lower urinary tract symptoms occur with age and may confound the effect of CCB therapy on LUTS and QOL in men. A five-year longitudinal study of men without previous LUTS

treatment demonstrated the slow nature of the disease progression. The mean IPSS increased from 4.6 to 5.5 (+20%; $P<0.0001$) over the five-year period, equating to a mean yearly increase in IPSS of 0.18.[37] In an attempt to adjust for the affect of the natural progression of LUTS, the difference in IPSS score prior to and following commencement of CCB therapy was reduced by 0.9. Those patients in whom the change in IPSS was less than 0.9 were attributed with a zero change in IPSS after commencing CCB therapy.

The patients were also administered a standard questionnaire to obtain information on their age; name, dosage and indication for their CCB; its duration of use; whether they suffered any medical conditions or had undergone any procedures which might affect LUTS, independent of the natural progression with ageing; and all the medications they had taken in the six months prior to participating in the study.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) Version 14.0. Summary statistics were analysed for each variable based on frequencies or means and standard deviations, depending on whether the variable was categorical or continuous. The Pearson correlation was used to measure the relationship between change in LUTS scores and age of patients, number of medical conditions known to cause LUTS and the use of drugs known to cause LUTS. The Pearson correlation was also used to measure the relationship between current LUTS scores and symptom diary scores. For differences between current and past LUTS scores, a paired sample *t*-test was used and a repeated measure ANOVA was also conducted to analyse whether the differences in LUTS over time varied according to presence of medical conditions known to cause LUTS, or other medication which may cause LUTS. In addition, to adjust for the natural progression of LUTS in men due to ageing a score of 0.9 was subtracted from the difference in IPSS scores used for the ANOVA and *t*-tests.

Results

A total of 38 male patients taking CCBs were enrolled in the study. All the 38 patients completed the two identical questionnaires (LUTS symptoms – IPSS; QOL questionnaire) to indicate if there were any differences between current LUTS and symptoms prior to commencement of CCB therapy, and any differences in QOL prior to and after commencement of CCB therapy.

The ages of patients ranged from 46.2 to 88.7 years, with the mean age of 66.9 years (95% CI: 63.9–69.9). Table 1 shows the distribution of participants' ages. The results of the study also showed that the most frequently prescribed class of CCB were the dihydropyridines (n=22; 55.0%) comprising four individual drugs; *amlodipine* (n=8; 20.0%), *felodipine* (n=6; 15.0%), *nifedipine* (n=4; 10.0%) and *lercanidipine* (n=4; 10.0%). The next most frequently prescribed class was the benzothiazepine, *diltiazem* (n=16; 40%), and the least prescribed class of CCB was the phenylalkylamine, *verapamil* (n=2; 5.0%). Two patients were each taking multiple (two) CCBs, with the remaining 36 patients taking single CCB therapy. Hypertension (n=30) was the

Table 1 Age distribution of the retrospective cohort

	Retrospective sample distribution	
Age(years)	*n*	Cumulative percentage
46–49	2	5.3
50–55	2	10.60
56–60	5	23.80
61–65	9	47.30
66–70	9	71.00
71–75	5	84.20
76–80	4	94.70
81–85	1	97.30
86–90	1	100.0
Total	38	100.0

leading indication for CCB use, followed by ischaemic heart disease (n=11) and management of arrhythmias (n=4). The majority had been taking CCB therapy for a period of five years or less (n=23; 60.5%) as shown in Table 2.

Twenty-seven (71.1%) of the 38 patients in the study reported suffering no other medical conditions that are known to cause LUTS apart from BPH. Seven (18.4%) patients had one other medical condition which may cause LUTS; one (2.6%) patient had two; and three (7.9%) patients had three other medical conditions.

Table 3 below shows the type and number of other medical conditions from which patients were suffering, and those who had undergone transurethral resection of the prostate (TURP) surgery, which may cause LUTS. Of the 11 patients who had other medical conditions that may cause LUTS, heart failure presented as the most common medical condition (n=5; 45.5%), followed by recurrent cough (n=4; 36.4%) and past history of TURP surgery (n=3; 27.3%); with stroke, spinal disc disorders and impaired mobility equally presenting as the least common medical conditions (n=2; 18.2%).

Prior to commencement of CCB therapy, the mean IPSS of the 27 patients with no other medical conditions that may cause LUTS was 2.63 (SD=2.70), with the mean IPSS being 4.63 (SD=3.96) for the 11

Table 2 Duration of calcium channel blocker therapy

Time period	Retrospective sample distribution		
	n[a]	Percentage[b]	Cumulative percentage[c]
<1 month	1	2.6	2.6
3–6 months	4	10.5	13.2
6–12 months	6	15.8	28.9
1–2 years	5	13.2	42.1
2–5 years	7	18.4	60.5
>5 years	15	39.5	100.0
Total	38	100.0	100.0

[a] number of patients
[b] percentage of patients
[c] cumulative percentage of patients

Table 3 Other medical conditions which may cause LUTS

Medical conditions	Retrospective sample	
	n*	Percentage** of cases (n=11)
Stroke	2	18.2
Spinal disc disorders	2	18.2
Congestive heart failure	5	45.5
Impaired mobility	2	18.2
Recurrent cough	4	36.4
TURP surgery	3	27.3
Total	18	163.8

* number of patients
** percentage of patients

patients with other medical conditions that may cause LUTS. After commencement of CCB therapy, the mean IPSS of the 27 patients with no other medical conditions that may cause LUTS was 7.44 (SD=5.69), with the mean IPSS being 12.2 (SD=5.23) for the 11 patients with other medical conditions that may cause LUTS. There was a non-significant correlation between change in IPSS and number of medical conditions (other than BPH) that may cause LUTS (Pearson correlation coefficient = 0.245, P=0.139), and whilst the difference in IPPS after commencement of CCB therapy was greater for those patients with medical conditions known to have caused LUTS this difference was not significant at a 0.05 level (F=3.2, P=0.082).

Of the 38 patients questioned, 23 (0.5%) patients were not taking any other medications which were known to affect bladder function, while 15 (9.5%) patients were. Twelve (31.6%) patients were taking one medication known to affect bladder function, two (5.3%) were taking two medications and one (2.6%) was taking three. These medications included atenolol (n=5), metoprolol (n=5), frusemide (n=4), dothiepin (n=2), digoxin (n=1), prazosin (n=1) and amiloride (n=1).

Prior to commencement of CCB therapy, the mean IPSS of the 15 patients taking other medications that are known to affect bladder function was 2.71 (SD=2.78). The mean IPSS was 3.38 (SD=3.96) for the 24 patients not taking other medications that are known to affect bladder function. After commencement of CCB therapy, the mean IPSS of the 15 patients taking other medications that are known to affect bladder function was 9.45 (SD = 5.03). The mean IPSS was 8.71 (SD=6.51) for the 23 patients not taking other medications that are known to affect bladder function.

There was no significant difference in the change of IPSS after commencement of CCB therapy between patients taking other medications that are known to affect bladder function and patients not taking other medications that are known to affect bladder function (F=0.734, P=0.397).

The mean IPSS prior to commencement of CCB therapy was 3.13 (95% CI: 2.09–4.17), indicating 'mild' LUTS (IPSS$\leq$7) under the AUA classification of degree of severity of LUTS, whereas the mean IPSS after commencing CCB therapy without adjustment for the natural progression of LUTS in men due to ageing was 9.82 (95% CI: 7.83–11.80), indicating 'moderate' LUTS (IPSS=8–19) (Figure 1). After adjusting for the natural progression of LUTS, paired sample statistics showed that there was a significant increase in the mean IPSS (5.85; CI: 4.26–7.45; P<0.001) after commencement of CCB therapy, indicating significant worsening of LUTS. Length of time on a CCB was associated with increased self-reported worsening of IPSS. In a regression analysis that controlled for prior LUTS score, age and medical conditions known to cause LUTs, length of time was significantly related to increased LUTS score across three time periods of less than one year, between one and five years and over five years – B=2.12 (95% CI: 063–4.17).

The QOL score illustrated worsening QOL with increasing total IPSS scores. The total scores ranged from a minimum of zero, indicating no adverse impact on the QOL, to a maximum of 19, indicating maximal adverse impact on the QOL. The mean QOL score prior to commencement of a CCB was 1.42 (95% CI: 0.86–1.99), and increased to 3.66 (95% CI: 2.49–3.66) after commencement of CCB therapy. Paired sample statistics showed that there was a highly significant increase in the mean QOL score (2.27; 95% CI: 1.40–

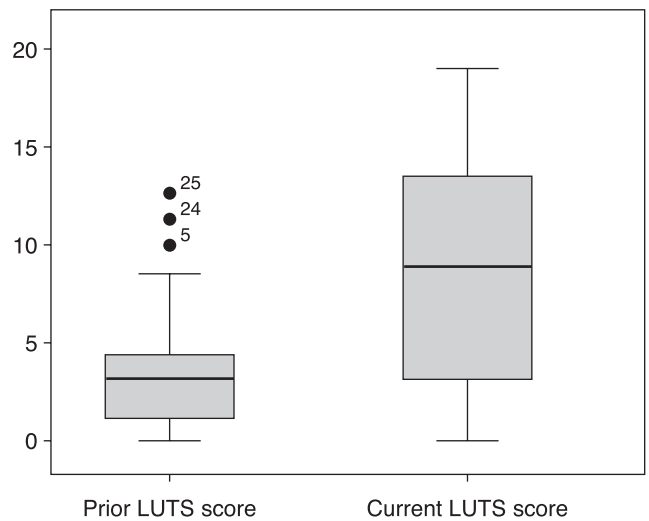

Figure 1 Mean IPPS scores pre- and post-commencement of a CCB

3.15, $P<0.001$) after commencement of CCB therapy, demonstrating significantly worsening QOL. A significant Pearson correlation coefficient of 0.595 ($P<0.001$) was observed, between a change in IPSS and QOL score which showed that worsening of the patients' QOL was correlated with their worsening LUTS after commencement of CCB therapy.

The linearity between the 'current' IPSS obtained from the patient answers in the questionnaire and the symptom diary completed by the patient as measured by the Pearson correlation coefficient was 0.554 ($P<0.001$), and demonstrated a significant correlation between the 'current' IPSS obtained from answering the questionnaire and the symptom diary. This supported the reliability of the patients' responses.

Discussion

The results, after adjustment was made for the natural progression of LUTS which occurs in men with BPH, showed a significant relationship between commencement of CCB therapy and worsening of LUTS in this retrospective study.

In this study there were no exclusion criteria, and therefore it is likely that there were a number of patients in the study who had little or no LUTS, and would not have been suffering from urinary obstruction. Given this fact, it is possible that if only males with a diagnosis of urinary obstruction were included in the study they may have shown an even greater worsening of LUTS after commencement of CCB therapy.

Even though the results of the study indicated a significant worsening of LUTS in males after the commencement of CCB therapy, it could be argued that if this worsening of LUTS did not have a negative influence on QOL for those patients, then the worsening of LUTS may not be of such concern. The findings of the study indicate that not only is there worsening of LUTS in males after the commencement of CCB therapy, but that the worsening of LUTS is accompanied by a significant reduction in the QOL of these patients.

Although there was a non-significant correlation between differences in IPSS and those patients with other medical conditions that could give rise to LUTS, the correlation does warrant further investigation. Of the 38 patients a considerable proportion had other conditions which may give rise to LUTS, for example stroke, heart failure, recurrent cough or previous prostate surgery. It must be noted that although the above-mentioned medical conditions may give rise to LUTS, it does not automatically follow that patients diagnosed with these medical conditions will experience LUTS. Nevertheless, consideration should be given to future studies using a larger sample size, excluding males with other medical conditions that may give rise to LUTS.

Previous research has highlighted the importance of extracellular Ca^{2+} entry through dihydropyridine-sensitive channels and mobilisation of intracellular Ca^{2+} for activation of the detrusor muscle.[11] L-type calcium channel blockers have a potent inhibitory effect on human detrusor muscle, but it has been demonstrated that different CCBs act at different receptor sites and have different therapeutic actions.[38] Accordingly, one may expect there could be differences in their adverse effect profile. Unfortunately, the sample size was too small to indicate any differences in CCB sub-class effects or any differences in the effects of individual CCB drugs within the sub-classes. As the functional properties of L-type calcium channels are modulated in a complex manner by CCBs that act on multiple sites, further studies, again with larger sample sizes, may delineate differences in effect, within CCB sub-classes or individual CCB drugs.

Further, this study was unable to show whether there were any differences in effect on those patients whose LUTS symptoms were primarily caused by detrusor overactivity compared with patients whose LUTS symptoms were primarily those of an obstructive nature with no or little detrusor overactivity.

This study relied upon the patients' recall of their symptoms prior to the commencement of their CCB, which in some cases was more than five years earlier, and we acknowledge that our findings are dependent on the patients' recall accuracy. However, this methodology is commonly used in retrospective studies; and we demonstrated that in the short term the participants' recall was reliable, based on the correlation between the IPSS responses and diary entries. It was found that the longer the duration of CCB treatment the greater the difference between prior and current LUTS scores, which could easily suggest that those on medication for longer may have overestimated their impact. However, the natural history of LUTS, particularly in males, is that they worsen with time, and the greater difference is also consistent with this.

The results of this study suggest that in middle-aged males the introduction of a CCB may be associated with worsening of LUTS, and an associated decline in QOL. This association needs to be assessed through prospective large-scale studies. However, given the common use of these agents in males to treat a range of cardiovascular conditions we would suggest men prescribed a CCB should be questioned about urinary symptoms before and after commencing treatment.

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CONFLICTS OF INTEREST

None.

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