

PB-PG-0107-12198 – NIHR Research for Patient Benefit Programme – Final report

Project title: Randomised, double blind, placebo controlled, crossover trial of the adjuvant properties of Imipramine for the overactive bladder

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Plain language summary

The aim of this study was to test the hypothesis that additional beneficial effects were achieved from Imipramine when combined with an antimuscarinic drug for the treatment of overactive bladder symptoms. We recruited 12 patients to the study.

This project ran into a fundamental problem that is good news for the patients but bad news for the study. In recent years we have discovered, as a result of a series of experiments, that a key underlying pathology affecting patients with overactive bladder is a hidden chronic urine infection. This arises because disease producing bacteria invade the urothelial cells of the bladder which they live in as a parasite and in a very dormant state. This means that they are not dividing very much and so they are not very susceptible to antibiotic attack. Being enclosed inside the cells they are also protected from immune activation.

Because of the nature of these infections they are not readily detected by the conventional means of urinalysis by dipstick or urine culture. We started to unmask these infections by using microscopy of fresh unspun urine to count the white blood cells. By these means we discovered a considerable number of patients with inflammatory bladder disease who had not previously been considered to suffer from urine infection. These patients described the symptoms of irritable bladder storage problems as typified by overactive bladder. They also exhibited resistance to treatment with an antimuscarinic agent and these were the very patients whom we were starting on combination therapy with imipramine to treat recalcitrant overactive bladder symptoms

With persistence of our research work we have found that we can identify significant infection through symptoms of urinating dysfunction and the culture of the spun urinary sediment supplemented by urinary cytokine (1) profiles and counting of the urothelial cells shed by the bladder into the urine.

Whilst the case still has to be rigorously tested, we started to treat patients who were suspected of harbouring such infections with antibiotics. Gradually it became clear that our outcomes had changed very significantly and that our patients with overactive bladder symptoms were responding to treatment in a way that we had never previously seen. A notable feature of the response was that affected patients, whilst still requiring an antimuscarinic drug to help manage their symptoms, displayed a response on a low dose of a single agent. This meant that the number of patients who were failing single therapy and would, in the past, have been considered for combination therapy using an antimuscarinic combined with Imipramine, fell. We did our best to recruit but the opportunities ceased to present, and the study was ended early.

(1) Cytokine: - A general term for non-antibody proteins released by a specific type of cell as part of the body's immune response

Keywords

Overactive bladder

Summary of research findings

Study Design

Proof of concept study. A randomised, double-blind, placebo controlled, crossover trial of the adjuvant properties of imipramine for the overactive bladder

Aim

The aim of this study was to use a randomised, double-blind cross-over design to test the hypothesis that Imipramine 25 mg nocte, added to antimuscarinic monotherapy for overactive bladder symptoms, is superior to placebo in the amelioration of these symptoms in adult patients.

Background

Overactive Bladder (OAB) symptoms affect 16.6% of people aged ≥ 40 years. OAB is independently associated with falls and fractures, urinary tract and skin infections, sleep disturbances and depression and is an extremely distressing symptom which, particularly amongst the elderly, can limit activities.

Atropine-resistant, nerve induced detrusor contractions have long been recognised and efforts are being made to find alternatives to the antimuscarinics. Attention focused on β_3 -sympathomimetic agents and P2X purinergic receptor antagonists. Botulinum toxin, superior to antimuscarinic agents, inhibits co-transmission of acetylcholine and ATP. Noradrenaline acting at β_3 sites inhibits detrusor contractions. Serotonin is also a known inhibitor of bladder contractions. It should be possible to augment the effect of an antimuscarinic by using another drug that works synergistically at these alternative targets, but will be some years before these molecules come out of development.

Imipramine hydrochloride has been used in the treatment of childhood enuresis for a long time and fifty six randomised trials of tricyclic drugs for nocturnal enuresis, involving 3624 children have been published. Over twenty years ago it was recommended as a treatment for the overactive bladder in adults, but efficacy was limited and it was superseded by the advent of oxybutynin and others of this class (1). Only one study of Imipramine in adults has been published, it was conducted in the elderly but was underpowered.

Imipramine inhibits reuptake of noradrenaline and serotonin equally. Changes in postsynaptic beta-adrenergic receptor sensitivity and increased responsiveness of the adrenergic and serotonergic systems contribute to the mechanism of action. The drug partially blocks ionic currents mediated through P2X receptor channels.

We have studied 130 patients (115 female, 15 male; mean age=58, SD=18) who had not responded fully to monotherapy using oxybutynin or tolterodine, even in doses in excess of those licensed. They were managed by the addition of Imipramine 25 mg nocte to their regime. This combination therapy induced a significant change in average daily frequency ($F=6.6$, $df=2$, $p=0.001$) but not average daily incontinence ($F=1.1$, $df=2$, $p=0.329$). The significant differences were also detected in a score of urgency symptoms. ($F=15$, $df=2$, $p<0.001$). Thus we identified marked synergy between imipramine and the unsuccessful antimuscarinic with good symptom relief and side effect profile. The add-on effect is not likely to be antimuscarinic. The data, albeit from an open observational experiment, was most encouraging all the more because patients persisted with treatment.

If found to be effective this treatment would change practice by offering a readily available alternative to pure antimuscarinic therapy, when this fails for the OAB. It is very cheap, so with the two main antimuscarinic agents off-patent, we could extend the therapeutic range with minimal additional cost.

The use of combination therapy in this manner would add a third stage to a simple well-validated, three stage treatment schedule; (1) clear pyuria, (2) bladder training and an inexpensive antimuscarinic (3) the latter, plus an inexpensive add-in. This would be ideally suited to Primary Care and by extending options it could reduce the referrals to Secondary Care. There are substantial safety data to encourage adoption. The costs are very low so the pharmacy committees should identify an advantage over newer me-too antimuscarinics.

Through five clinical trials, we have shown that the cross-over design works well with the overactive bladder. It is possible to achieve a fully informative efficacy study, producing unequivocal, clinical and statistical results, from a single centre. By promoting this method, we seek to encourage an expansion of drug evaluation studies arising from clinical services, independent of industry, and in the interests of the NHS.

Primary Outcome

Change in urinary urgency score

Secondary outcome

Change in average 24-hour frequency

Change in average 24-hour incontinence

Change in I-QOL score

Patients preference for treatment

Record of any side effects

Method

Patients recruited to either Group A [Imipramine 25mgs + antimuscarinic for 6 weeks – 2 week Wash-out on antimuscarinic monotherapy - Placebo + antimuscarinic for 6 weeks] or Group B [Placebo + antimuscarinic for 6 weeks – 2 week Wash-out on antimuscarinic monotherapy – Imipramine 25mgs + antimuscarinic for 6 weeks]

Inclusion criteria: adult patients aged ≥ 18 years with symptoms of overactive bladder; frequency ≥ 8 per 24 hours, urgency and/or urge incontinence who are on treatment with a single antimuscarinic agent.

Patients were instructed on how to complete and maintain a frequency/volume urinary diary chart and asked to measure their voided volumes during three days of any seven-day diary data collection period. Patients were checked and treated for urine infection before being enrolled.

Results

12 patients recruited in total. Unable to recruit anymore. This is explained in detail in Section 5 above.

We shall conduct an analysis of the data collected thus far. A publication would be very unlikely unless the data revealed a striking difference.

Patient and public involvement

Clearly this study is not going to contribute much in this realm. However, our experiences in interacting with patients presenting with overactive bladder and other lower urinary tract symptoms, who would normally have been eligible for this study if a urine infection had not been detected has been Damascene. The poor patients suffer dreadfully because their symptoms are so much at variance with the results of the routine urinalysis. They are turned away by the medical services because their tests are negative when in fact they are suffering from a very significant urinary tract infection. They sense this and the psychological consequences are severe. To contribute to a re-balancing of the public understanding of the subject we are going to set up a website with a Blog dedicated to the widespread misunderstandings about lower urinary tract symptoms. We have the scientific evidence available now to contradict the popular misconceptions with some considerable authority. The study was set up to respond to recalcitrant overactive bladder and whilst our hypothesis did not get tested as we had hoped, it is now redundant because we have found a means of getting these people better. We are going to invest effort in ensuring that the wider public is made aware of this.

Data sharing statement

See link

[\[https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253\]](https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253) for the NIHR position of the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

Disclaimer

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This final report has not been peer-reviewed. The report was examined by the Programme Director at the time of submission to assess completeness against the stated aims.

This project was carried out between May 2008 and April 2012