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The role of ondansetron in the management of cholestatic or uraemic pruritus – a systematic review

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Abstract

Context

Pruritus associated with hepatic or renal failure can be a troublesome symptom, refractory to treatment, associated with significant physical and emotional distress, and reduction in quality of life for patients already burdened with chronic disease. Serotonin has been implicated as a possible pathological mediator, and therefore 5HT₃ antagonists have been suggested as a possible therapeutic intervention.

Objectives

This review of the literature systematically explores the role of ondansetron in the management of cholestatic or uraemic pruritus.

Methods

Electronic databases were systematically searched for randomized controlled trials (RCTs) examining the role of ondansetron in cholestatic or uraemic pruritus between 1966 and 2008.

Results

Five RCTs were included in this systematic review: three for cholestatic pruritus, and two for uraemic pruritus. All trials examined ondansetron versus placebo, however with differing treatment protocols. Overall, three studies showed no benefit to ondansetron over placebo, however two studies in cholestatic pruritus showed small reductions in pruritus with questionable clinical significance.

Conclusion

Ondansetron was demonstrated to have negligible effect on cholestatic or uraemic pruritus on the basis of a limited number of studies.

Key words

Ondansetron, 5HT₃ antagonists, itch, pruritus, cholestasis, hepatic failure, uraemia, renal failure

Running title

Ondansetron for pruritus

Introduction

The pruritus associated with hepatic or renal failure can be a further disabling symptom in people already dealing with chronic or life-limiting illnesses. Chronic pruritus can be persistent and distressing with significant effects on physical comfort and quality of life, with potential psychological, functional and social impact and increased morbidity.¹⁻³ The pathophysiology of this pruritus is not well understood, however is thought to be driven by chronic inflammation involving dedicated unmyelinated C fibres, similar to but distinct from pain fibres, stimulated by one or more peripheral pruritogens. Mediators suspected to be involved in this process include histamine, endogenous opioids and serotonin.^{2,3} Furthermore, in cholestasis, bile salts, steroid hormones and their metabolites, and lysophosphatidic acid have been implicated,³ whilst in uraemia chronic skin changes, calcium-phosphorus products, hyperparathyroidism, and dialysis efficacy may influence pruritus.²⁻⁴

Pharmacological strategies to try to manage itch have targeted these proposed pathophysiological mechanisms, and have included antihistamines, antidepressants, membrane-stabilisers, rifampicin, thalidomide, opioid antagonists and 5HT₃ antagonists. Because of the proposed involvement of serotonin in mediating the pruritus of cholestasis and uraemia, 5HT₃ antagonists have been tried for symptom management. The Australian Therapeutic Guidelines for Palliative Care⁵ recommend sedating antihistamines, doxepin, and paroxetine. In cholestasis, they also suggest rifampicin and ondansetron. The evidence for these recommendations is limited largely to case reports, case series and under-powered clinical trials.

The Australian Palliative Care Clinical Studies Collaborative (PaCCSC) was commissioned to evaluate the role of ondansetron for chronic pruritus. This systematic review is the first step of a process to explore the need for further or more complex adequately powered phase III studies. Therefore the aim of this paper is to systemically examine the evidence for the use of ondansetron in the management of pruritus secondary to cholestasis or uraemia.

Methods

Search strategy for the identification of studies

An initial search of MEDLINE, PubMed, EMBASE and CINAHL was undertaken in October 2008 using the key words: ondansetron, cholestatic itch, cholestasis, pruritus, antipruritics and combinations of these. Searches were limited to studies in humans. Results from the four databases were merged into one file and duplicate results deleted from the merged file.

Eligibility criteria

Only randomized controlled trials comparing the effect of ondansetron to placebo on cholestatic or uraemic pruritus in humans were considered. Only published trials in English were considered.

Methods of review

Two authors independently assessed the abstracts of studies retrieved from the initial search. Abstracts that meet the eligibility criteria were identified for full text retrieval and analysis. The references of full text articles retrieved were hand searched to

identify any other relevant articles. Trial quality was assessed using Jadad scores.⁶ Differences were settled by consensus. Other data collected included the number and characteristics of the participants, the 5HT₃ antagonist dose, administration route and schedule, outcome measures and results. Given the disparate nature and extent of the studies identified, and the quality of their reporting, adherence to the CONSORT guidelines was not evaluated.

Results

There were 241 studies identified using the search method, and of those, 80 were selected for full text retrieval. Of the 80 papers retrieved only six studies were randomised controlled trials. One study was published in Turkish, leaving only five studies eligible for review (see Table 1). There were no further relevant articles identified by hand search of the references of the retrieved papers. Significant heterogeneity was identified in study design, underlying diagnosis, route of administration of ondansetron, dosage and duration of intervention, and outcome measures. Given these factors it was not possible to combine the data into a meta analysis.

Patient population and setting

Three of the eligible studies examined the role of ondansetron in cholestatic itch, and two studies in uraemic itch (see Table 1).

Ninety-one patients were assessed across the five studies, with an average age of participants in each of the study groups ranging from 47 to 60 years (overall range of 27-80 years), and 37% male participation ranging from 16-28% (n=11) in cholestatic itch, and 54-63% (n=23) in uraemic itch.

For the cholestatic group, one study had predominantly patients with primary biliary cirrhosis, whilst the other two studies had more heterogenous aetiologies. The average bilirubin was 17-63µmol/L in the three studies, with a very large range (5-1250µmol/L). For the uraemic group, the aetiology of the renal failure and the frequency of haemodialysis was listed in one study, but not the other.

Intervention

The protocols for the use of ondansetron varied significantly. The protocol with the largest number of participants was oral ondansetron/placebo 8 milligrams (mg) three times daily followed a washout period and crossover. However the duration of the therapeutic trial before washout and crossover varied from five days to four weeks. The study by O'Donohue *et al.* varied from this by using a loading intravenous ondansetron /placebo dose followed by oral maintenance ondansetron/placebo with no crossover.⁷

Outcome measures

Four studies used 0-10 visual analogue scales (VAS), most commonly reporting mean pruritus ratings, however one study reported median ratings,⁸ and another distinguished mean pruritus and mean peak pruritus ratings.⁹ Another study used a 0-10 numerical rating scale (NRS), and also incorporated a subjective assessor-rated

pruritus score using a 0-3 NRS.¹⁰ These outcome measures were rated once, twice or three times daily.

Two studies also used a measure of scratching activity using a fingernail mounted piezo-electric crystal.^{7,10} Two studies incorporated measurement of additional antihistamine use (one oral, one topical) as a surrogate for improvement in pruritus.^{8,9}

Outcomes

One study found no difference in VAS assessed uraemic pruritus with ondansetron.⁸ Two studies found reductions in VAS assessed cholestatic and uraemic pruritus by 21 and 16% with ondansetron, however this was matched by reductions in the placebo group of 22 and 25% respectively.^{7,11} In contrast, one study showed a modest improvement of 1.34 points in peak VAS assessed cholestatic pruritus with ondansetron compared to placebo,⁹ and one study showed minimal improvement of 0.21 points in mean NRS assessed cholestatic pruritus.¹⁰ Five of thirteen participants also had a 27% decrease in subjective assessor-rated pruritus on a 0-3 NRS, with the remaining eight showing no difference with placebo.¹⁰ The duration of treatment did not affect the likelihood of response.

In the studies that measured scratching activity, there was no correlation between scratching activity and VAS, and there was no reduction in scratching in the ondansetron group compared with placebo.⁷ Whilst one study showed a small reduction in NRS assessed pruritus, there was no associated reduction in scratching activity.¹⁰

There was no reduction in the use of rescue oral or topical antihistamine as an outcome in the two studies that examined this.^{8,9}

Toxicity was not addressed in one study,¹¹ whilst two studies stated no adverse effects documented.^{8,9} However two studies describe high rates of constipation (44-71%), as well as cramps, nausea, headache and dizziness as may be expected from a 5HT₃ antagonist^{7,10}

Discussion

In a number of small studies with heterogeneous populations, methods and outcomes, there is no evidence for the benefit of ondansetron in the management of uraemic pruritus, and scant evidence in cholestatic pruritus. For the two studies that demonstrate benefit in cholestatic pruritus, the effect is small and debatable as to the clinical significance to the patient.

Treatment with placebo produced significant reductions in subjective pruritus ratings. Whilst this effect may be frequently encountered in trials with subjective symptom based outcomes, this makes the demonstration of effect of ondansetron more difficult as the benefit needs to be of a magnitude sufficient to have clinical benefit over and above the placebo response.

Objective measurements of scratching activity have been shown to correlate with visual observation.^{12,13} Some studies have also demonstrated correlation between objective

scratching activity and subjective symptom ratings,^{14,15} however, scratching activity does not always correlate with subjective symptom ratings.^{16,17} This highlights the complex relationship between subjective and objective measures which is not unique to itch, but is seen in many symptom related studies, such as pain. For the patient, whilst subjective improvement is important, it's relationship to objective measurements remains variable and a major challenge for research.

Generalisability

The reported studies only evaluated stable patients with persistent pruritus in the ambulatory setting. It is not possible to comment on patients with pruritus associated with acute hepatic or renal failure – whilst the underlying mechanism may be similar, in chronic pruritus there may be central sensitization, as seen with chronic pain states, that make persistent pruritus different pathophysiologically and potentially more refractory to treatment.¹⁸

Limitations

Any systematic review is limited by the studies available. Despite evidence of use in clinical practice, the underlying studies to support ondansetron for this indication are few and inconclusive, thus making it hard to draw absolute conclusions. Given the magnitude and direction of change, even if a meta-analysis were possible, it is unlikely to show any net clinical benefit.

The two studies of uraemic pruritus were published in 2000 and 2003. Progress in the management of chronic renal impairment and haemodialysis may mean that the symptom profile and responsiveness to treatment of patients on haemodialysis may be different from those described in these studies. For instance, modern day dialysis dose, flux and management of haemoglobin, calcium, phosphate and parathyroid hormone levels may lead to better dialysis efficacy and reduced secondary hyperparathyroidism with subsequent reduced symptom burden. However there is no indication from these studies that ondansetron has a role in uraemic pruritus.

Reporting of toxicity was very poor in all studies, given the rates of toxicity reported in the use of 5HT₃ antagonists in more than single dose studies in oncology and peri-operative care.

Implications for practice

Management of cholestatic or uraemic pruritus should first look to optimize the treatment of the underlying condition. However optimization may not be possible or sufficient to ameliorate the pruritus. Given the multifactorial nature of pruritus and the paucity of evidence for effective treatments, treatment may involve a number of modalities including topical, systemic and non-pharmacological strategies based on the underlying aetiology. For cholestatic pruritus, consideration should still be given to antihistamines, cholestyramine, rifampicin, opioid antagonists, selective serotonin reuptake inhibitors and bright-light therapy.^{2,3} For uraemic pruritus, therapeutic trials could include emollients, capsaicin, antihistamines, gabapentin, tricyclic antidepressants, thalidomide, opioid antagonists, acupuncture and ultraviolet phototherapy.^{2,4}

Implications for research

Further work is required to understand the pathophysiology of pruritus in both acute and chronic cholestatic and uraemic pruritus in order to understand therapeutic targets for intervention.

There is a paucity of randomised controlled trials in therapeutic interventions for cholestatic or uraemic pruritus. This is further complicated by the difficulties with measuring pruritus subjectively and objectively, and high placebo response rates. Given these difficulties, and findings of this systematic review, the results do not support the pursuit of further randomised trials of ondansetron in the treatment of cholestatic or uraemic itch.

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Table 1. Randomised controlled trials of ondansetron in cholestatic or uraemic pruritus.

RCT – randomized controlled trial, PBC – primary biliary cirrhosis, HD – haemodialysis, VAS – visual analogue scale, NRS – numerical rating scale

	Design	n	Age (range)	Male	Characteristics	Intervention	Outcomes	Jadad
Muller et al. 1998 ⁹ (Austria)	RCT with crossover	18	Mean 60 (31-73)	5/18 (28%)	PBC 6/18, hepatitis C 6/18, alcoholic cirrhosis 3/18, cryptogenic cirrhosis 2/18, HCC 1/18 Mean bilirubin 37µmol/L (range 11-760)	Ondansetron/placebo 8mg tds po for 7 days then crossover	VAS 0-10 tds (mean & peak)	4
Ashmore et al. 2000 ⁸ (United Kingdom)	RCT with crossover	16	Median 60 (28-77)	10/16 (63%)	HD (mixed aetiology) 9pts HD 3x/wk, 7pts HD 2x/wk	Ondansetron /placebo 8mg tds po for 14 days then crossover	VAS 0-10 daily (median); rescue antihistamine use	3
Murphy et al. 2003 ¹¹ (United Kingdom)	RCT with crossover	17	Median 59	13/24 (54%)	HD (unspecified aetiology) No information on HD frequency	Ondansetron/placebo 8mg tds po for 14 days then crossover	VAS 0-10 bd (mean)	4
O'Donohue et al. 2005 ⁷ (United Kingdom)	RCT	18	Mean 55 (27-80)	3/19 (16%)	PBC 17/19 Mean bilirubin 63µmol/L (range 10-1250)	Ondansetron/placebo 8mg IV bolus then ondansetron/placebo 8mg bd po for 5 days	VAS 0-10 3hrly (mean); scratching activity	4
Jones et al. 2007 ¹⁰ (Netherlands)	RCT with crossover	14	Mean 47 (29-63)	3/14 (21%)	PBC 7/14, chronic hepatitis 4/14, other 3/14 Mean bilirubin 17µmol/L (range 5-113)	Ondansetron/placebo 8mg tds po for 4 weeks then crossover	Assessor severity 0-3; Self-report NRS 0-10 daily (mean); scratching activity	4