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Review

New agents for the medical treatment of interstitial cystitis

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Interstitial cystitis (IC) is a painful, sterile, disorder of the urinary bladder characterised by urgency, frequency, nocturia and pain. IC occurs primarily in women but also in men with recent findings indicating that chronic, abacterial prostatitis may be a variant of this condition. The prevalence of IC has ranged from about 8 - 60 cases/100,000 female patients depending on the population evaluated. About 10% of patients have severe symptoms that are associated with Hunner's ulcers on bladder biopsy; the rest could be grouped in those with or without bladder inflammation. Symptoms of IC are exacerbated by stress, certain foods and ovulatory hormones. Many patients also experience allergies, irritable bowel syndrome (IBS) and migraines. There have been various reports indicating dysfunction of the bladder glycosaminoglycan (GAG) protective layer and many publications showing a high number of activated bladder mast cells. Increasing evidence suggests that neurogenic inflammation and/or neuropathic pain is a major component of IC pathophysiology. Approved treatments so far include intravesical administration of dimethylsulphoxide (DMSO) or oral pentosanpolysulphate (PPS). New treatments focus on the combined use of drugs that modulate bladder sensory nerve stimulation (neurolytic agents), inhibit neurogenic activation of mast cells, or provide urothelial cytoprotection, together with new drugs with anti-inflammatory activity.

Keywords: *chondroitin sulphate, histamine-3 receptors, hyaluronic acid, inflammation, interstitial cystitis, mast cells, pain, quercetin*

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1. Introduction

IC is a syndrome that appears to occur primarily in women with symptoms of urinary frequency, urgency, nocturia and suprapubic/pelvic pain [1-4]. However, IC occurs also in males [5] and recent evidence suggests that chronic non-bacterial prostatitis and prostatodynia may be a variant of IC [6,7]. It was originally thought that the prevalence of IC may be about 6 - 18 women/100,000 [3,8,9]. In the first study to report prevalence of IC, a regional population was used in Finland and the criteria included [8]:

- Frequency of pain for many months, without relief
- Bladder biopsy infiltration
- Bladder overdistention providing temporary relief of symptoms

The incidence was reported to be 18.1 cases per 100,000 females [8]. The prevalence of IC was also determined in the Netherlands [10], but in this case, the pathology of the bladder and the presence of increased bladder

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mast cells were the main criteria, in this case, the prevalence was calculated to be 8 - 16 cases/100,000 female patients [10]. A similar attempt in the USA was made from invited responses from urologists who diagnosed IC by:

- Painful bladder for months
- Absence of infection or other causes
- Presence of glomerulations under cystoscopic examination following bladder distension under general anaesthesia [9]

This prevalence was estimated at about 40 cases/100,000 female patients. Only 1/5 of all the women who had been classified as having 'painful bladder syndrome' with sterile, non-bacterial urine were included [9]. Recent population based data in the USA relied on the Nurses' Health Study (NHS) I and II (USA) which started in 1976 and 1989, respectively [11], and provided a higher estimate of about 60 cases/100,000 in women [11]. In this study, however, no definitive or uniform diagnostic criteria were used and the prevalence was calculated on 63 'confirmed' cases of IC of which 16% were definitive, 56% probable and 29% possible [11]. Such differences may be due to the use of different 'diagnostic' criteria (see below) or differences between European and American patient populations, possibly reflecting differences in genetic, dietary or environmental factors, as well as patient and physician awareness.

Most IC patients appear to be young and middle aged women who usually have periods of symptomatic flares and remissions [1-4]. IC also occurs in adolescents and children [12]. The symptoms worsen periodically in 40 - 50% of premenopausal women and common triggers include psychological or physical stress. In 75% of women, sexual intercourse appears to exacerbate their symptoms [13]. Many women with IC have gynaecologic symptoms, such as chronic pelvic pain (CPP) or dyspareunia and IC should be suspected in women with CPP who have negative laparoscopic evaluations. Over 50% of IC patients have symptoms or history of allergic problems and about 30% have concurrent diagnosis of IBS [14,15]. Due to these findings, IC has been considered a neuroimmunoendocrine condition [13]. The symptoms of IC create substantial psychological, social and emotional problems for affected patients, many of whom describe their pain as 'migraine of the bladder.'

Diagnosis of IC is usually based on a history of irritative voiding symptoms (polyuria, nocturia), pain and negative urine cultures. Certain criteria were established [16] for research studies by the USA NIH and include:

- Positive medical history for at least three months
- Negative urine cultures
- Cystoscopic evidence of ulcers or mucosal haemorrhages (glomerulations) during bladder hydrodistention under general or spinal anaesthesia and bladder biopsy is included in order to exclude other bladder pathology, such as tuberculosis or transitional carcinoma

The potassium sensitivity test has been proposed as a marker of epithelial permeability and is apparently positive in 70% of IC patients [17]. The more common non-ulcer variety is found in almost 90% of IC patients and is characterised by petechial bladder mucosal haemorrhages (glomerulations) without ulceration. However, recent papers have shown that glomerulations may occur in non-IC patients and they do not correlate with the degree of inflammation [18]. Patients with non-ulcer disease have minimal evidence of chronic inflammation on biopsy [19]. IC patients have recently been grouped in two subcategories, those with inflammation on biopsy and those without; the former group usually presents with more pronounced symptoms who, however, reported better relief with bladder distention [20]. In those patients with bladder inflammation, the urine has been reported to have increased levels of IL-6 [20,21], while the bladder wall had increased expression of ICAM-1 [22,23]. Bladder biopsies from IC patients also contained an increased number of mast cells, many of which were positive for IL-6 and/or stem cell factor (SCF) [24,25].

The treatment of IC presents a challenge for clinicians since the cause(s) of the disease is unknown and is generally considered to be multifactorial in origin. Various aetiologies have been postulated but the prevailing hypotheses are:

- Altered bladder permeability through some damage to the bladder protective glycosaminoglycan (GAG) layer
- An increase in the numbers and activation of bladder mast cells
- IC sensory nerve sensitisation with tachykinin release

Due to this lack of knowledge of the pathophysiology of IC, treatment is frequently empirical. A variety of systemic, intravesical, cystoscopic and surgical treatments have been used.

The goal of treatment is to control or ameliorate symptoms while providing support and understanding to the patient. Some patients note that their IC symptoms are provoked by certain items in their diet, such as caffeine, alcohol or acidic foods [2]. Dietary provocation of symptoms is patient-specific and when noted, patients fair well when they avoid these items.

The passive bladder hydrodistention at the time of diagnostic cystoscopy provides temporary (usually 2 - 3 months) symptomatic relief in 20 - 25% of patients and may be repeated as an elective 'therapeutic' procedure [26]. Intravesical DMSO [27] had been the main course of treatment until recently. The most commonly reported therapeutic modalities, as recently tabulated by the Interstitial Cystitis Database, were cystoscopy with hydrodistention, oral amitriptyline and intravesical heparin [26]. Patients usually prefer oral therapy to intravesical therapy as the first approach to treatment. Most of the drugs discussed below (**Table 1**) need to be prospectively studied in placebo-controlled, randomised studies employing a validated Symptom and Problem scoring index, such as the one described by O'Leary and Sant [28].

2. Analgesics

IC patients frequently experience pain. Pain is classified into nociceptive, somatic, neuropathic and visceral. Somatic pain is generally thought to be more responsive to analgesics, such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Neuropathic pain is related to aberrant somatosensory activation and is usually described as burning and/or constant; this type of pain responds better to anti-epileptic and antidepressant drugs. Visceral pain is related to injury or inflammation to internal organs, such as the bladder and has a cramping, diffuse quality. IC pain appears to have both neuropathic and somatic components.

Many patients have symptoms suggestive of a neuropathic pain component. This type of pain could arise from either direct damage of pain nerves in the bladder or prolonged stimulation of bladder nerve endings, leading to changes at the spinal cord level. This possibility is strengthened by the recent reports of ATP-driven pain receptors in mouse bladders [29] through action on $P2X_3$ receptors [30]. In view of the fact that pain is a major component of IC symptomatology, a number of the available long-acting opioids could and should be tried in patients with IC. These include dihydrocodeine (DHC plus), MS-Contin or Oramorph SR, as well as transdermal phentanyl (Duragesic). The analgesic potency of these drugs has been compared for effective interchange [31]. It should, however, be kept in mind that morphine and certain other opioids stimulate mast cell secretion [32] and could potentially complicate the clinical picture. There are a number of other opioid and non-opioid analgesics that have been tried in IC patients, but for which the available data are not yet sufficient to ascertain their effectiveness in IC (**Table 2**).

2.1 Gabapentin (Neurontin™)

Anti-epileptic drugs have been used to treat a variety of chronic pain syndromes, including headache, trigeminal neuralgia, post-herpetic neuralgia, diabetic neuropathy and cancer pain [33]. A meta-analysis of their use in chronic pain included a number of studies with patients achieving 50% or better pain relief [33]. This study concluded that anti-epileptic medications are effective in the treatment of trigeminal neuralgia, diabetic neuropathy and migraine prophylaxis.

In a recent double-blind, randomised, placebo-controlled trial, gabapentin was more effective than placebo for post-herpetic neuralgia [34] and diabetic neuropathy [35]. Two IC patients were recently reported to improve functionally with reasonable pain control [36]. Any anecdotal reports from IC patients are hard to evaluate, especially since gabapentin is typically increased over time and the maximal appropriate dose has not been established for IC. Nevertheless, the gabapentin adverse effect profile is better than that of other anti-epileptic or tricyclic antidepressants that have been used for treatment of neuropathic pain syndromes.

2.2 Mexiletine (Mexitie™)

Mexiletine is an oral anti-arrhythmic drug with analgesic effects similar to the local anaesthetic lignocaine [37]. Lignocaine has been used effectively to treat neuropathic cancer pain by sc. administration of the affected area; this approach was helpful where oral mexiletine had failed [38]. Mexiletine may potentially help control the pain in IC patients and avoid the risks of chronic opioid analgesic usage, but

Table 1: New pharmacological treatment options.

Category		Mechanism	Major adverse effects
Analgesics	Gabapentin (Neurontin™)	Antiseizure	
	Mexiletine (Mexitie™)	Oral 'local' anaesthetic	Retention
	Pentazocine (Talwin™)	Opioid	Retention
	Prochlorperazine (Compazine™)	Anti-emetic	Drowsiness
	Propiram (Dirame™)	Opioid	Retention
	Tramadol (Ultram™)	Non-opioid central acting	↑ Seizure risk, anti-depressants, nausea
Antidepressants	Amitriptyline (Elavil™)	Tricyclic NE/5HT uptake inhibitor	Sedation
	Desipramine (Norpramin™)	Tricyclic NE/5HT uptake inhibitor	Sedation
	Doxepin (Sinequan™)	Tricyclic NE/5HT uptake inhibitor	Sedation
	Imipramine (Tofranil™)	Tricyclic NE/5HT uptake inhibitor	Sedation
Antihormones	Leuprolide acetate (Lupron™)	GnRH agonist	'Menopause state'
	Tamoxifen (Nolvadex™)	Oestrogen-receptor antagonist	'Menopause state'
Anti-inflammatory agents	Celecoxib (Celebrex™)	COX-2 inhibitor	Diarrhoea
	Choline magnesium trisalicylate (Trilisate™)	COX-inhibitor	GI upset
	Chondroitin sulphate + Quercetin (Algonot-Plus™)	Proteoglycans	None known
	Dipyrone (Novalgin™)	COX-inhibitor, spasmolytic	Agranulocytic anaemia ($1/10^6$)
	Rofecoxib (Vioxx™)	COX-2 inhibitor	Diarrhoea
Leukotriene (LT) blockers	Montelukast (Singulair™)	Leukotriene receptor antagonist	Headache, vasculitis
	Zafirlukast (Accolate™)	Leukotriene receptor antagonist	Headache
	Zileuton (Zyflo™)	Leukotriene synthesis inhibitor	↑ Serum levels of propranolol, warfarin
Immunosuppressive agents	Cyclosporin (Neoral™)	IL-2 receptor antagonist	Nephro, hepatotoxicity
	Etanercept (Embrel™)	TNF soluble receptor (human)	↑ Susceptibility to infection, headache
	Infliximab (Remicade™)	TNF-α soluble antibody	
	Methotrexate	Folic acid synthesis inhibitor	Chilitis, ↓ blood counts
Mast cell mediator release/action inhibitors	Cimetidine (Tagamet™)	Histamine-2 receptor antagonist	Reversible impotence
	Cromolyn (Intal™, Gastrocrom™)	Mast cell 'stabiliser'	GI upset
	Hydroxyzine (Atarax™, Vistaril™)	Histamine-1 receptor antagonist	Sedation
	Indolinone derivatives (SUGEN™)	Tyrosine kinase inhibitors	Not in humans
	IPD-1151T	Immunoregulator	None reported
	Quercetin (in Algonot-Plus™)	Flavonoid	None known
Mucosal surface protectors	Chondroitin sulphate + quercetin (Algonot-Plus™)	Proteoglycan and flavonoid	None known
	Heparin	Proteoglycan (intravesical)	↑ Chance of bleeding
	Hyaluronic acid (Cystistat™)	Proteoglycan (intravesical)	None known
	Pentosanpolysulphate (Elmiron™)	Synthetic polysaccharide	GI upset, alopecia
	Prostaglandin E (Misoprostol™)	Prostaglandin E_1 analogue	Diarrhoea
Neuropeptide receptor antagonists	Resiniferatoxin (?)	Capsaicin analogue (intravesically)	Mild irritation
	CP-96,345 (Pfizer)	NK-1 receptor antagonist	Phase I trials
	SR-48,968 (Sanofi)	NK-2 receptor antagonist	Phase I trials
	SR-48,692 (Sanofi)	Neurotensin-receptor antagonist	Phase II trials

Table 1: New pharmacological treatment options.

Category		Mechanism	Major adverse effects
Neurolytic (antineuronal)	Antalarmin (NIH)	Corticotropin-releasing hormone	Not in humans
	Astressin (Neurocrine)	Receptor antagonists	Not in humans
	BP 2-94 (Bioprojet)	Histamine-3 receptor agonist	Not in humans
	Tizanidine (Zanoflex)	α-2 Receptor agonist	Impotence, mast cell activation
Other	BCG	Immunostimulant	Autoimmunity
	Doxorubicin (Adriamycin™)	Antineoplastic agent	Cardiotoxicity
	L-Arginine	Amino acid nitric oxide (NO) precursor	None known
	Octreotide (Sandostatin™)	Somatostatin analogue	↑ Mast cell activation

Table 2: Analgesics that may be useful in IC.

		Main characteristics
Opioids	Pentazocine (Talwin™)	High potency, fewer adverse effects
	Propiram fumarate (Dirame™)	Post-operative pain
	Tramadol (Ultram™)	Non-addictive
Non-opioids	Gabapentin (Neurontin™)	Anti-epileptic
	Mexiletine	Local anaesthetic
	Prochlorperazine (Compazine™)	Antipsychotic

it must be used with caution in patients with a history of cardiovascular pathology. Alternatively, mexiletine could be added to the intravesical 'cocktail' used in certain centres [26].

2.3 Pentazocine (Talwin™)

Pentazocine is a mixed opioid receptor agonist-antagonist with potent analgesic action. It could theoretically be useful in IC especially because it does not induce mast cell secretion [31]. The latter adverse effect is a common problem with many opioids, especially morphine [32] and could potentially aggravate symptoms especially in a sub-population of patients with bladder mastocytosis.

2.4 Prochlorperazine (Compazine™)

This drug is a dopamine receptor antagonist used for the treatment of nausea and vomiting associated with early pregnancy. It has also been reported to have analgesic properties, especially in migraines [39]. It could prove to be useful in IC, especially because it also affects smooth muscle hyperactivity.

2.5 Propiram fumarate (Dirame™)

Propiram fumarate is a new orally administered opioid analgesic used mostly for post surgical pain. This drug at 50 mg was comparable to 60 mg of codeine sulphate in relieving moderate postoperative pain [40]. Moreover, propiram fumarate was effective in moderate to severe pain associated with gynaecological procedures [40]. Its onset of action appears to be quicker than that of codeine and has longer duration. Adverse effects included dizziness, drowsiness, nausea and vomiting.

2.6 Tramadol (Ultram™)

Tramadol is a centrally acting drug with multiple mechanisms of analgesic actions. A major mechanism involves activation of the μ opioid receptor subtype with analgesic potency roughly equivalent to that of acetaminophen with codeine, but without the addictive or adverse effects of other opioids [41]. Another possible mechanism involves increase in synaptic levels of serotonin and noradrenaline however, neither mechanism sufficiently explains the analgesic potency. The most common adverse effects are dizziness/vertigo, nausea and headache in about 30% of patients in 30 days [42], nausea can be reduced if the dose is increased slowly. The most serious adverse effect could be an increased incidence of seizures (10% of patients over a 30 day period) which could be more pronounced in patients also taking serotonin re-uptake inhibitors, opioids, neuroleptics and monoamine oxidase (MAO) inhibitors.

3. Antidepressants

A number of clinical trials have shown that the tricyclic antidepressants, but not the most recent serotonin specific re-uptake inhibitors (SSRIs), are beneficial in chronic pain [43]. Tricyclic antidepressants have been used in IC, based on their anticholinergic, analgesic, antihistaminic and sedative, as well as antidepressant effects [16,43]. Some of these drugs also inhibit mast cell secretion [44,45] an action that may possibly explain their benefit in IC. Some reports indicated that tricyclic antidepressants may promote the growth of melanoma in animals but these were considered too premature and conflicting to warrant any change in prescribing policies [46].

3.1 Amitriptyline (Elavil™)

Amitryptyline, a well known tricyclic antidepressant, is effective in relieving the pain of post-herpetic neuralgia [47] and chronic facial pain [48]. One open label study of 25 IC patients who had failed standard therapy were prescribed amitriptyline. They were started on 25 mg before bedtime and the dose was increased over a month to 75 mg at bedtime [49]. Twenty IC patients tolerated the maximum dose, eight patients experienced total remission, 11/19 had diminished urinary urgency and 8/9 reported relief of dyspareunia [49]. In another study, 22 patients (12 male and 10 females) with urinary symptoms reminiscent of IC but without IC, were studied. Eleven patients had complete remission on amitriptyline up to 100 mg per day, with six more reporting improvement [50]. The usual starting dose of amitriptyline is 25 mg orally at night. This is then increased in 25 mg increments on a weekly basis and titrated up until a therapeutic response is achieved usually at 75 mg per day. Side effects occur in 20 - 30% of patients when doses reach 75 mg or higher and include weight gain, irritability and palpitations. Symptoms return in most patients upon discontinuation of the medication. Tricyclic antidepressants have not been studied in randomised placebo-controlled trials in IC.

The mechanism of analgesic actions of amitriptyline in general and particularly in IC, is not known. Its well known anticholinergic and sedative effects would be useful in IC as they may reduce frequency and nocturia. Some evidence indicates that they may reduce secretion from sensory and other nerve endings, thus reducing neuropathic pain. Amitryptyline has also been reported to inhibit mast cell secretion [45,51] which may provide an alternative or complimentary explanation.

3.2 Desipramine (Norpramin™)

Desipramine but not fluvoxamine, showed a significant analgesic effect in a randomised, double-blind, placebo-controlled, crossover study of ten healthy volunteers [43]. In two randomised, double-blind studies in patients with diabetic neuropathy, desipramine was as effective as amitryptyline, while the SSRI fluoexetine was no more effective than placebo. Desipramine also relieved post-herpetic neuralgia in a clinical trial with similar design [52].

3.3 Doxepin (Sinepuan™)

Doxepin was shown to relieve chronic back pain in randomised, double-blind comparisons to placebo [53]. There may be reason to prefer doxepin to amitriptyline because doxepin has the additional benefit of being both a histamine-1 and histamine-2 receptor antagonist, properties used for the treatment of systemic mastocytosis [54]. Doxepin, like amitriptyline, has also been reported to inhibit mast cell secretion [45,51] a possible additional benefit in IC.

3.4 Imipramine (Tofranil™)

Imipramine was shown to be beneficial in painful diabetic neuropathy in a small double-blind, crossover study [55]. Like desipramine, imipramine is a well known tricyclic antidepressant; however, both have strong anticholinergic effects and dry mouth that often preclude their long term use as they may also precipitate urinary retention in high doses. Neither drug has been studied adequately in IC.

4. Antihormones

IC symptoms appear to worsen perimenstrually [13]. Such symptoms are often mistaken for pelvic inflammatory disease or endometriosis [1,14]. Female sex hormones are known to upregulate immune processes, while allergic conditions worsen perimenstrually [56]. Oestradiol also augmented mast cell secretion *in vivo* [57] and that induced by substance P (SP) *in vitro* [58], as well as bladder mast cell secretion *in situ* [59]. Moreover, bladder mast cells in IC exhibited increased expression of oestrogen receptors [60]. Oestrogens were shown to induce proliferation of bladder mast cells.

Table 3: Anti-inflammatory drugs that may be useful in IC.

COX inhibitors		Main characteristics
COX-1/2 inhibitors	Choline-magnesium trisalicylate (Trilisate™)	Reduced GI effects
	Dipyrone (Novalgin™)	Smooth muscle relaxant
COX-2 inhibitors	Celecoxib (Celebrex™)	Few GI adverse effects
	Rofecoxib (Vioxx™)	Few GI adverse effects
Leukotriene (LT) blockers	Montelukast (Singulair™)	LT receptor antagonist
	Zafirlukast (Accolate™)	LT receptor antagonist
	Zileuton (Zyflo™)	LT synthesis inhibitor

4.1 Leuprolide acetate (Lupron™)

This agent stimulates the hypothalamus to induce an initial release of gonadotropins, followed by a prolonged period of female hormone depletion [61]. Leuprolide acetate has typically been used for the treatment of endometriosis [61]. However, it has also been reported to nearly eliminate the pain associated with inflammatory bowel disease in 75% of patients [62]. However, it has not been tried in IC. This drug induces a state of menopause with the possibility of hot flushes and irritability.

4.2 Tamoxifen (Nolvadex™)

Tamoxifen is an oestrogen receptor antagonist that has been used extensively for the treatment and, more recently, the prophylaxis of breast cancer [31]. IC bladder mast cells express oestrogen receptors [60,63] and oestradiol pretreatment increases carbachol and SP-induced bladder mast cell secretion [59]. These effects are blocked by oestrogen [58]. Blockade of oestrogen receptors on bladder mast cells or other immune cells may reduce their activation and subsequent contribution to IC symptoms. This drug will induce a state of menopause with hot flushes and irritability. Tamoxifen has not been tried in IC.

5. Non-steroidal anti-inflammatory agents

IC has long been considered an inflammatory condition of the bladder. However, recent reports indicate that only a portion of IC patients have demonstrable bladder inflammation (see Introduction). Moreover, in a recent study of 69 patients with documented IC the presence of inflammation did not correlate with the severity of the cystoscopic findings observed during hydrodistention with anaesthesia [2,18]. In fact, even the cystoscopic appearance of IC bladders has been challenged as glomerulations were also reported to be as frequent even in non-IC bladders.

A number of studies investigated levels of various inflammatory molecules in urine, but there was no conclusive evidence for any elevations, except possibly IL-6 [21]. Nevertheless, it seems reasonable to investigate the possibility of using NSAIDs (**Table 3**) at least in those patients who have evidence of bladder inflammation. However, it should be kept in mind that most NSAIDs are associated with increased risk of gastrointestinal bleeding [64]. Moreover, there are some reports that such agents may also stimulate histamine release [65].

5.1 Celecoxib (Celebrex™)

COX-1 is a constitutively expressed enzyme localised in a wide variety of tissues with little difference in mRNA levels between inflamed and normal tissues. In contrast, COX-2 expression is induced by several inflammatory mediators, including IL-1 and TNF-α [66]. Prostaglandins, synthesised by COX-1 and COX-2, sensitise nociceptor nerve endings (many of which contain SP) leading to chronic, inflammatory pain. Celecoxib has been shown to be effective in the treatment of osteoarthritis [64,67]. It is also approved for rheumatoid arthritis, acute pain and menstrual pain. The gastrointestinal toxicity of the COX-2 inhibitors is less than that of the common non-steroidal anti-inflammatory drugs [64]. In addition, COX-2 inhibitors do not decrease production of thromboxane and do not increase bleeding time.

5.2 Choline magnesium trisalicylate (Trilisate™)

This is a combination of salicylate with choline and magnesium that renders it well-tolerated even at high doses. This formulation is often given to elderly patients. Due to the presence of magnesium, there is less likelihood of allergic histamine release from

human leukocytes, previously reported with NSAIDs [65].

5.3 Chondroitin sulphate + quercetin (Algonot-Plus™)

This combination is discussed under 7.4 and 8.1 below.

5.4 Dipyrone (Novalgin™)

Dipyrone (or metamizole) is an old NSAID that never made it to the USA. It has greater analgesic potency and better profile than other drugs in its class, especially since it has strong spasmolytic activity. For instance, it has been effectively used for the treatment of trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain and IBS [68]. Unlike other NSAIDs, dipyrone is not associated with serious gastrointestinal bleeding. Agranulocytic anaemia is a notable adverse effect that may develop in 1 per million cases [69]. This adverse effect was considered critical enough to preclude this drug from the US market. Yet, another NSAID diclofenal (Voltaren) is commonly used in the USA even though it causes aplastic anaemia, an anaemia where all bone marrow cells are destroyed with a higher incidence of 1 per 100,000 cases [69]. In any event, dipyrone could be of benefit in IC because it could not only provide analgesia, but it would relax the detrusor muscle with associated reduction in urgency and frequency.

5.5 Rofecoxib (Vioxx™)

A number of studies demonstrated that rofecoxib was effective in the treatment of postoperative dental pain and osteoarthritis, with rofecoxib being superior to placebo in all measures of analgesic efficacy [66]. Rofecoxib (50 mg) was shown to have analgesic effect roughly equivalent to that of 400 mg ibuprofen but rofecoxib had longer duration of action [66]. Rofecoxib was associated with lower incidence of gastrointestinal adverse effects than non-selective COX inhibitors [67]. Moreover, rofecoxib did not increase intestinal permeability. As with celecoxib, this drug may be useful only in patients with documented bladder inflammation.

5.6 Leukotriene (LT) blockers

Leukotriene 'blockers' could theoretically be of benefit in IC patients with bladder mastocytosis. However, published evidence from random IC patients does not support its use as arachidonic acid products were not elevated in urine from IC patients [21]. Montelukast (Singulair™) is a leukotriene D (LTD_4)-receptor antagonist for maintenance of mild-to-moderate asthma [70]. As leukotrienes are involved in allergy and inflammation, such drugs could be useful especially in patients with documented bladder mastocytosis and history of allergies and asthma. Taken together with steroids, it can reduce their requirement but, Churg-Strauss vasculitis has been reported. It is the only drug of its category used only in children. It is also the only drug used once per day [70]. Zafirlukast (Accolate™) is a leukotriene receptor antagonist used for mild-to-moderate asthma. Concurrent administration increases serum concentrations of theophylline. This drug could potentially be useful in patients with bladder mastocytosis and concurrent allergic reactions or asthma. Zileuton (Zyflo™) is an inhibitor of leukotriene synthesis useful for the maintenance treatment of asthma [71]. However, this particular drug has to be given four times per day; moreover because it is metabolised by P450, it can increase serum concentrations of propranolol, theophylline, warfarin and other drugs.

6. Immunosuppressive agents

Some evidence suggests that IC may have an autoimmune aetiology. As a result, a variety of oral immunosuppressive drugs have been tried or may potentially be useful in IC.

6.1 Cyclosporin (Neoral™)

Cyclosporin is a well known immunosuppressive agent used in organ transplants. Cyclosporin inhibits T-cell activation and subsequent cytokine release by inhibiting the calcium-dependent phosphatase calcineurin. Calcineurin acts by dephosphorylating a transcription factor which is required for IL-2 activation of T-cells [31].

In an open label study of 11 patients with intractable IC, cyclosporin was used for 3 - 6 months in an initial dose of 2.5 - 5.0 mg per kg po., followed by a maintenance dose of 1.5 - 3.0 mg per kg po. daily [72]. Micturition frequency and bladder pain were improved significantly, while patients were taking the drug and so did the voiding volumes. Bladder pain decreased or disappeared in 10/11 patients [72]. However, symptoms recurred in the majority of patients after cessation of treatment. The use of such

immunosuppressive agents may be more helpful in those patients with documented bladder inflammation by biopsy.

Alternatively, the action of cyclosporin may be related to inhibition of allergic conditions, in particular mast cell activation [73] and proliferation [74].

6.2 Etanercept (Embrel™)

Tumour necrosis factor (TNF-α) is well known to participate in inflammation [75]. Inhibition of TNF action has emerged as a powerful way to inhibit inflammation for the treatment of conditions, such as rheumatoid arthritis [75]. Etanercept, a soluble human TNF receptor given subcutaneously, was approved for rheumatoid arthritis. Adverse effects include headache and increased susceptibility of pulmonary infections [76].

6.3 Infliximab (Remicade™)

Infliximab is a chimeric human/mouse TNF blocking monoclonal antibody recently approved for iv. treatment of rheumatoid arthritis and inflammatory bowel disease [76]. Adverse effects also include headaches, increased susceptibility to infections and infusion reactions, such as fever and urticaria. Neither etanercept nor infliximab have so far been reported as having been used in IC.

6.4 Methotrexate

Methotrexate is a well known antimetabolite interfering with folic acid metabolism by inhibiting tetrahydrofolate reductase [31]. It is commonly used for the treatment of leukaemias, as well as rheumatoid arthritis [31]. A recent study investigated the safety and efficacy of methotrexate in nine women with refractory IC [77]. There was significant reduction in pain in 4/9 women, but no reduction in urinary frequency or voided volume was noted [77].

7. Mast cell mediator release/ action inhibitors

More than half of IC patients have been reported to have a history of allergic problems, including asthma [15,78]. In a recent study, 5/6 patients with IC had symptoms of allergic conditions with high bladder mast cell and eosinophil counts; the mean bladder biopsy histamine in these patients was 17.7%, as compared with 8.9% in IC patients without allergic symptoms and 4.5% in non-IC controls [79]. Most importantly, intravesical allergic provocation was positive in 4/5 patients with allergic symptoms and the prognosis of these patients was generally better [79]. We also reported on an IC patient with chronic urticaria [78].

The role of the mast cell in the pathophysiology of IC has been extensively documented [15]. Over 50% of IC patients have a demonstrable increase in the number of bladder mast cells, nearly 80% of which have increased activation [80-82]. Recent publications investigated mast cell subtypes in the bladder of IC patients using immunocytochemistry and reported that the TC (tryptase-chymase) positive cells were primarily increased [83]. It was further shown that bladder mastocytosis was more prominent in 'classic' IC with 6- to 10-fold mast cell increase, as compared with a two-fold increase in non-ulcer IC [25]. These activated bladder mast cells appeared different from those seen in anaphylaxis and may release inflammatory mediators without degranulation [63,82,84]. The histamine metabolite methylhistamine [85,86] and the unique mast cell protease, tryptase [87] were reported to be elevated in the urine of IC patients. An experimental model of autoimmune cystitis was characterised by oedema, perivascular lymphocytic infiltrations and 100% detrusor mast cell accumulation four weeks after immunisation [88]. Elsewhere, it was concluded that mast cells mediate the severity of experimental cystitis, as intravesical administration of SP or *Escherichia coli* lipopolysaccharide in W/W^v mast cell deficient mice did not result in demonstrable oedema, leukocyte infiltration or haemorrhage [89].

Mast cells release many molecules, especially cytokines, such as IL-6 [90-92] that could participate in inflammation [93] and be relevant to IC pathophysiology [94]. For instance, histamine and TNF induce vascular permeability, kinins and prostaglandins are nociceptive, chymase and tryptase cause tissue damage and cytokines promote inflammation [94]. It is still not entirely clear what triggers bladder mast cell activation in the absence of demonstrable allergy. Nevertheless, it was reported that antigen challenge of sensitised rhesus monkey bladder strips led to contractions and histamine release which were blocked by pretreatment with an anti-human IgE monoclonal antibody [95]. Moreover, bladder hydrodistention led to a histamine-to-creatinine ratio that was increased in the urine of IC patients, as compared with controls [96].

SP is increased in the bladder of IC patients [97] as is the expression of SP receptor (NK_1) mRNA [98]. In addition, the neuropeptides neurotensin (NT) and SP are released from bladder nerve endings in acute psychological stress [99,100]. The bladders from IC patients express more oestrogen receptor positive mast cells [63] and the addition of oestradiol increased activation of mast cells by carbachol [59] and SP [58]. Nerve growth factor (NGF) levels are increased in the urinary bladder of women with IC [101,102], strengthening the notion that there is increased input from the peripheral sensory nervous system [103-105] and neuron-mast cell interactions [63,106,107]. Recent evidence indicated that CNS invasion by pseudorabies virus induced neurogenic cystitis that was associated with bladder mast cell activation in the rat [108]. Moreover, sympathetic nerve degeneration/depletion in rats was shown to lead to mast cell hyperplasia and increase in histamine of the affected dura [109], suggesting an aetiology similar to that of sympathetic dystrophy. This finding is important in view of the fact that dura mast cells have been implicated in the pathophysiology of migraines [110], migraines occur more often in IC patients with allergies [111] and IC patients often describe their pain as 'migraine' of the bladder. Inhibition of bladder mast cell secretion may, therefore, be a useful therapeutic strategy in IC.

7.1 Cimetidine

Cimetidine is a histamine-2 receptor antagonist [31]. Cimetidine has recently been used more commonly in IC, possibly because of its usefulness in reducing stomach acidity in relation to the stress associated with IC, as well as the use of steroids and NSAIDs. It has been reported to alleviate some of the symptoms of IC [112,113] but this drug has not been evaluated in randomised, placebo-controlled studies. There may be reason to combine cimetidine with hydroxyzine as cimetidine has been reported to increase plasma levels of hydroxyzine [114] due to cimetidine's inhibition of liver P450 enzyme metabolism [31]. However, it should be kept in mind that cimetidine's inhibitory effects on liver metabolism lead to gynaecomastia and reversible impotence [31] which would be a problem in male IC patients.

7.2 Cromolyn (Gastrocrom™)

Cromolyn is a 'mast cell stabiliser' that has been used for allergic asthma and rhinitis (Intal™), as well as for food allergy (Gastrocrom™) [115]. Intravesical cromolyn sodium, a mast cell stabiliser, showed promise in an early study but responses were short-lived. Cromolyn is unlikely to be effective because it does not inhibit mucosal mast cells (MMC) [116,117] and its action is very short-lived due to rapid tachyphylaxis [118].

7.3 Hydroxyzine (Atarax™, Vistaril™)

There is some evidence that certain antihistaminic compounds may also have analgesic properties [119]. Hydroxyzine is a well known heterocyclic histamine-1 receptor antagonist [120], the only side effect of which is sedation, which can be overcome after one week of continuous daily use [121].

Hydroxyzine also inhibits histamine [51] and β-hexosaminidase release from mast cells [122], as well as neurogenic activation of bladder mast cells [123]. Other antihistamines, including the newer non-sedating antihistamines, such as the hydroxyzine metabolite cetirizine (Zyrtec™) [122], did not have any inhibitory effect. An open-label study using visual analogue scales for symptoms and overall response was conducted using 50 mg hydroxyzine at bedtime. Of 140 patients who took the drug, 95 patients returned the evaluations with about 40% improvement in symptoms, as self-reported by the patients [124]. As more than 50% of IC patients appear to have a history of allergic problems [15,78], it was interesting to note that this response rose to 55% in IC patients with bladder mastocytosis on biopsy and/or a history of allergies [125].

Due to its sedating properties, hydroxyzine is given at night [121]. Usually, morning sedation disappears when the drug is given daily for more than one week. The typical starting dose is 25 mg po. at night for 1 - 2 weeks, followed by increasing doses in 25 mg increments depending on tolerance of the patients. If patients cannot tolerate a starting dose of 25 mg, they can start with a 10 mg pill or elixir (5 mg per teaspoon). Most patients see therapeutic benefit at doses of 50 - 75 mg at night after three months of sustained use.

A small clinical trial was funded by the ICA (Interstitial Cystitis Association, USA) to be conducted at Tufts-New England Medical Centre's General Clinical Research Centre under an Investigational New Drug (IND) application (#51,574 to TCT) approved by the FDA on 17 September 1996. Before the pilot study could be initiated, the NIDDK (USA) established an IC Treatment Trials Group (ICTTG) that approved a five centre clinical trial to test hydroxyzine with or without

PPS against a double placebo. This study is currently ongoing.

Hydroxyzine could be combined with opioids because it may increase analgesia [126,127], while reducing morphine's adverse effects, such as hypotension due to opioid stimulation of mast cell histamine secretion [32]. Another drug that could be added to hydroxyzine in the acute setting is prochlorperazine (Compazine™), a well-tolerated anti-emetic drug (discussed above) that has been shown to have analgesic properties on its own and can be used as a suppository [39].

Our findings with mast cells may also be applicable to chronic non-bacterial prostatitis [128]. For instance, IC has been documented in men [5,7] and mast cell activation, similar to what has been reported in IC, was reported in a male patient with sterile bladder and prostate inflammation [6]. Mast cells are known to exist in the prostate and were shown to be significantly activated in experimentally induced prostatitis [129].

7.4 Indolinone derivatives

Intense immunoreactivity for stem cell factor (SCF, or c-kit ligand) has been reported in the human bladder [130]. Recent evidence indicates that bladder mast cells in IC patients may have an abnormality in c-kit (stem cell factor) expression [24,25,131], as well as in neurofibromatosis [132]. These findings, coupled with the high number and extent of activation of bladder mast cells in IC, indicate that IC may be a form of local mastocytosis.

C-kit mutations leading to abnormally high levels of CSF or c-kit expression have been identified in systemic mastocytosis [133-135]. It is, therefore, of interest that certain indolinone derivatives (SU4984, SU6577 and SU5614) killed neoplastic mast cells expressing a mutated *kit* that was constitutively activated [136]. Such drugs may be useful in patients with established bladder mastocytosis.

7.5 IPD-1151T

IPD-1151T is a new immunoregulatory drug that suppresses allergic processes regulated by helper T lymphocytes in particular, it decreases IgE production and eosinophilic inflammation [137]. This agent was orally administered (300 mg per day) for 12 months in 14 IC patients, 13 of whom had classic IC; there was significant improvement in bladder capacity, as well as of urinary urgency, frequency and lower abdominal pain along with a reduction in blood eosinophils and IgE [137].

The results of this study support the involvement of allergic processes. However, this study also used a small number of patients without being blind and without a placebo arm, making difficult to make any definitive statements about therapeutic prospects.

7.6 Quercetin in Algonot-Plus™

One unique class of natural compounds is the flavonoids that occur in plants and have potent anti-oxidant, cytoprotective and anti-inflammatory activities [138]. Many of these flavonoids inhibit inflammatory cell functions, basophil histamine release, as well as proliferation and activation of human lymphocytes. Certain flavonoids, such as quercetin, also inhibit mast cell secretion [138-140] and proliferation [138,141]. Their mechanism of action depends on a particular pattern of hydroxylation of their B ring [138,141] and is related to the phosphorylation of a 78 kDa protein [118] that was name MACEDONIA (MAst CEll DegranulatiON Inhibitory Agent) [94]. This protein was cloned recently [142] and was shown to be homologous to Moesin (Membrane Organizing Extension Spike proteIN) which belongs to a family of proteins now considered to regulate stimulus-response coupling [143].

Quercetin is one of the most commonly studied flavonoids [138]. It is found in citrus fruit pulp and many seeds, especially in olive seed oil [144]. It has been shown to inhibit mast cell proliferation [141] and activation [141] including allergic stimulation of human mast cells [145]. Quercetin also inhibits mucosal mast cells, while cromolyn does not [116,140]. Quercetin (500 mg orally twice-daily) was also recently used in a prospective, randomised, double-blind, placebo-controlled trial of patients with chronic prostatitis [146]; 67% of those with chronic prostatitis (n = 17) had significant improvement as compared with those on placebo (n = 13) [146]. The combination of the flavonoid quercetin with the proteoglycan chondroitin sulphate (Algonot-Plus™) was shown to have additive mast cell inhibitory activity.

8. Mucosal surface protectors

One of the theories to explain the pathophysiology of IC has been the existence of a defective GAG bladder layer [147], leading to a 'leaky' bladder epithelium

[148]. This premise was supported by the fact that intravesical protamine increased urea absorption in rabbit bladders, presumably due to protamine damaging or neutralising the GAGs protective abilities; this defect was reversed by intravesical pretreatment with the synthetic polysaccharide PPS. Moreover, urine hyaluronic acid was higher in IC patients, as compared with controls, indicating loss of this protective molecule [149]. Total urine glycosaminoglycans were also decreased in the urine of IC patients, even though they appeared to be unchanged when normalised to creatinine [150]. The theory behind a defective GAG layer and ways to 'coat' the bladder epithelium as a way of treating IC have been reviewed repeatedly. There is also recent evidence that bladder epithelial cells from patients with IC produce an inhibitor of heparin-binding epidermal growth factor, thus preventing necessary cell proliferation [151].

Some recent studies have challenged the defective GAG theory. Intravesical radiolabelled technetium was shown not to be differentially absorbed from the bladder of IC patients [152] and the GAG layer ultrastructural appearance was similar to that of controls [107]. Instead, the beneficial effect of the glycosaminoglycans may derive from inhibition of bladder mast cell activation, since mast cell proliferation and activation has been amply documented [13,15]. For instance, some publications (see below) reported that heparin may have 'anti-allergic properties' [153,154]. The same was also recently shown for PPS [155] and chondroitin sulphate [156].

Alterations in the GAG component of the protective mucin coating of the bladder urothelium may permit urine substances, such as potassium to penetrate the bladder wall resulting in mast cell activation, inflammation, sensory-nerve depolarisation and development of the symptoms of IC.

8.1 Chondroitin sulphate (in Algonot-Plus™)

This molecule is one of the most common natural proteoglycans [157]. It is a surface recognition site and a major component of human mast cell secretory granules [158,159]. Chondroitin sulphate has been used, together with the monosaccharide glucosamine for the treatment of osteoarthritis, with potential benefit as indicated by a recent meta-analysis [160]. We recently showed that chondroitin sulphate is also a potent inhibitor of mast cell secretion [156].

Pre-incubation of rat peritoneal mast cells with chondroitin sulphate (10^{-4} M) resulted in inhibition of histamine release in response to secretagogue compound 48/80 (0.1 μg/ml used for 30 min at 37°C) that increased with time and reached a maximum of 76.5% ($p = 0.0004$) by 10 min [156]. In contrast, the inhibitory action of the 'mast cell stabiliser' drug cromolyn decreased rapidly if pre-incubation lasted for more than 1 min [156]. The inhibitory effect of chondroitin sulphate extended to stimulation of rat CTMC by the neuropeptide SP, as well as by immunoglobulin E and anti-IgE; this inhibition also showed a dose-response relationship [156]. The possibility that the mechanism of action of chondroitin sulphate may be mediated through an effect on the availability of intracellular calcium ions was investigated and was shown that chondroitin sulphate inhibited calcium ion levels significantly. The extent of the inhibitory effect on intracellular calcium ion levels was confirmed with image analysis [156].

There are a number of problems however, with the presently available chondroitin sulphate food supplement preparations:

- There is no standardisation in their content of chondroitin sulphate C, D or E which vary in their size and degree of sulphation.
- The absorption is extremely low (< 5%) making it unlikely that sufficiently therapeutic levels will be reached.
- The most common source is cow's trachea with its inherent risk of spongiform encephalopathy ('mad cow disease').

In fact, the recent report of the independent panel commissioned by the British government to investigate the BSE outbreak, concluded that the problem was way underestimated [161].

A safe alternative is the new product Algonot-Plus™ that combines chondroitin sulphate from shark cartilage with the flavonoid quercetin. This patented formulation uses olive seed oil to prepare the solution, thus improving its absorption considerably. Moreover, it combines the well-known benefits of olive oil, which is rich in bioflavonoids [144] with many cytoprotective properties [162].

8.2 Heparin

Intravesical heparin has been reported to be one of the most common treatments of IC [26]. Treatment

with intravesical heparin (10,000 units in 10 ml sterile water) three times per week for three months resulted in clinical remission of symptoms in 27 of 48 patients (56%) and the remission was maintained in 80 - 90% of patients for up to one year if they continued maintenance intravesical heparin therapy [163]. Heparin presumably mimics the protective properties of the bladder GAG mucosal lining. An alternative or complimentary action could be through an inhibitory effect on bladder mast cells [153,154].

Heparin is one of the major constituent of mast cell secretory granules and it had been reported to inhibit mast cells and allergic reactions [153,154].

8.3 Hyaluronic acid (Cystistat™)

This molecule is a natural proteoglycan found in connective tissue and in human mast cell secretory granules [164]. Sodium hyaluronate prepared from rooster crowns has been used as a device to replenish joint viscosity by intra-articular injection, especially in osteoarthritis. A recent publication also reported increased urine hyaluronic acid in IC patients [149]. Based on this finding that supports the assumption that the bladder epithelial GAG lining is defective in IC, the glycosaminoglycan sodium hyaluronate (Cystistat™) was instilled intravesically in a group of 25 patients with refractory disease [165]; the drug dosage was 40 mg weekly for four weeks, followed by monthly administration. By 14 weeks, about 70% of patients had a positive response (complete and partial combined) but the response decreased after six months. There was no significant toxicity or morbidity. In another open label study, ten patients received 40 mg intravesical sodium hyaluronate weekly for six weeks, then monthly; however, this time only 30% responded [166].

Human mast cells express the isoform CD44 on their surface which binds to hyaluronic acid [167]. Based on these findings, rats were pre-treated intravesically with a 0.4% sodium hyaluronate solution for 30 min prior to acute immobilisation stress; there was significant inhibition of bladder mast cell activation, mast cell protease I and IL-6 [168]. As with heparin, part of the action of sodium hyaluronate may be mediated through inhibition of bladder mast cells.

8.4 Pentosanpolysulphate (PPS, Elmiron™)

Oral PPS sodium was approved in the USA under the 'Orphan Disease Act' and it is a synthetic polysaccharide that presumably replenishes the defective GAG layer. PPS consists of a negatively charged polysaccharide ester backbone (a polyanion) with some properties of sulphated glycosaminoglycans and an affinity for mucosal membranes.

Pilot studies of intravesical PPS administered twice weekly (300 mg in 50 ml of normal saline) for three months led to significant improvement in 40% of the PPS-treated patients as compared with 20% of the placebo group; there were no important side effects [169].

Double-blind placebo-controlled studies had reported improvement greater than 25 and 32% in patients on PPS compared with 13 and 16% in the placebo groups [170,171]. No significant side effects or complications were reported. However, alopecia occurred in 2.5% and nausea, vomiting and other gastrointestinal side effects in about 10% of patients. Several weeks of treatment (usually 12 - 16) are needed for symptomatic relief. A meta-analysis of four studies using PPS in IC conclusively demonstrated that it was significantly better than placebo in the treatment of pain (n = 398), frequency (n = 60) and urgency (n = 306), nocturia was not significantly affected [172]. Presently, there is one multi-centre clinical trial (funded by NIDDK, USA) with a four-arm design comparing hydroxyzine, PPS and their combination against a double placebo. PPS was also shown to be effective for chronic non-bacterial prostatitis.

Another possible or complimentary beneficial action of PPS could be an inhibitory effect on mast cells. We recently showed that pretreatment with PPS had a time- and dose-dependent inhibitory effect on rat mast cell histamine secretion [155]. This effect was associated with an inhibition of intracellular calcium ion levels otherwise triggered by the mast cell secretagogue compound 48/80 [155].

8.5 Prostaglandin E_1 analogue (Misoprostol™)

The oral prostaglandin E_1 analogue, Misoprostol™, is commonly used for stomach protection against the erosive effects of NSAIDs [66]. In one open label study of 25 IC patients receiving 600 mg po. daily for three months, 56% had significant symptomatic improvement [173]. Symptom response was assessed using a voiding log and a symptom score index. However, there was a high incidence (64%) of side effects, especially diarrhoea, even though they were considered minor.

9. Neuropeptide depletors/ receptor antagonists

Mounting evidence indicates that in IC there is proliferation of bladder nerves [103,105] containing sensory neuropeptides [105] or nerve growth factor [101,102], both of which are associated with pain and detrusor hyperactivity. For instance, there was increased presence of bladder neurons positive for vasoactive intestinal peptide (VIP) and peptide Y (NPY) [105], as well as for SP [97]; SP receptor mRNA was also shown to be increased in the bladder of IC patients [174]. There appeared to be an association of these neuronal processes to bladder mast cells [104,106]. Additionally, indirect support of the possible involvement of SP and other neuropeptides comes from different types of experiments:

- SP, NKA, VIP and bradykinin all stimulated histamine release from the isolated guinea-pig urinary bladder [175]
- Acute distension of the female rat urinary bladder depleted VIP, NPY that was correlated to the transient benefit obtained from the bladder hydrodistention in IC patients [176]
- Tachykinin receptor antagonists reduced xylene-induced cystitis in rats [177]
- SP induced microvascular leakage in the rat urinary bladder [174]
- SP is well known to activate mast cells [13,178,179]
- CNS-induced neurogenic cystitis was associated with bladder mast cell degranulation in the rat [108].

9.1 Resiniferatoxin

Capsaicin, the main ingredient in chilli peppers that acutely depletes sensory nerve endings [180], reduced pain, urgency and frequency by 50% and the rabbit bladder content of SP [181]. Such an effect could also be produced by the potent, chemical mast cell secretagogue compound 48/80. Also, mice lacking the capsaicin receptor had impaired nociception [182]. Intravesical capsaicin may have therapeutic benefit in IC as it was reported to relieve pain in patients with hypersensitive disorders of the lower urinary tract [183]. However, it is likely to have an immediate burning sensation and has not been tested in any controlled trials in IC. A new analogue of capsaicin, Resiniferatoxin (RTX), may be almost 1000 times as potent as capsaicin with much less burning pain typically associated with capsaicin [184]. RTX has been used intravesically for the treatment of overactive bladder [185], as well as bladder 'hypersensitive' disorder with pain [186]. The effect of RTX on bladder desensitisation was long lasting with absence of irritative symptoms [187].

9.2 Neurokinin (NK) receptor antagonists

The use of selective NK receptor antagonists is desirable. NK_1 receptors were documented in the rat urinary bladder and the non-peptide selective NK_1-receptor antagonist CP-96,345 (Pfizer) blocked urinary bladder plasma extravasation [188]. This SP-receptor antagonist also inhibited rat intestinal inflammation and rat mast cell protease II (RMCP-II) release from rat ileal explants exposed to *Clostridium difficile* toxin A. The NK_2 receptor antagonist GR87389 competitively antagonised human detrusor contractions. Neurokinin A induced contractions of the dog urinary bladder were blocked by the NK_2 receptor antagonist SR-48,968 (Sanofi) [189]. NK_2 receptors were also identified in the human bladder [2]. The possible involvement of mast cell-derived products in neurogenic bladder is supported by the fact that intravesical administration of PGE_2 in conscious female rats induced micturition, an effect blocked by pretreatment with selective NK_1 and NK_2-receptor antagonists [190]. Unfortunately, NK_1 receptor antagonists have generally failed to show significant analgesic effect in humans [191].

9.3 Neurotensin (NT) receptor antagonists

The non-peptide NT-receptor antagonist SR-48,692 (Sanofi) was shown to inhibit stress-induced rat bladder mast cell activation [100]. This antagonist also inhibited immobilisation in stress-induced colonic secretion of mucin, PGE_2 and RMCP-II [192], as well as isolated mast cell stimulation [193]. NT is known to stimulate secretion from rat peritoneal [194], as well as human jejunal mast cells. What is of particular interest with respect to the pathophysiology of IC is the finding that the effect of NT may be mediated by some SP-receptor dependent process as NT inhibited SP-induced histamine release from rat peritoneal mast cells [195]; conversely, NT-induced mast cell activation in colonic explants was also blocked by the NK-1 receptor antagonist CP-96,345.

10. Neurolytic agents

Corticotropin-releasing hormone (CRH) receptor antagonists (or CRF, for factor) is well-known for being secreted rapidly under stress and stimulates the hypothalamic-pituitary-adrenal (HPA) axis [196]. CRH is also released outside the brain, such as from dorsal root ganglia (DRG) [196] and from immune cells [197] where it has pro-inflammatory actions [198] by stimulating tissue mast cells [199,200]. Acute stress triggers bladder mast cell activation, an effect mediated by both NT and SP [100,201]. CRH-receptor antagonists could, therefore, be useful in blocking these peripheral pro-inflammatory effects of CRH or its structural natural analogue, urocortin. In fact, urocortin was more potent that CRH [200] in triggering skin mast cell secretion and vascular permeability [199].

10.1 Antalarmin

Antalarmin is a non-peptide, non-selective CRH-receptor antagonist, originally synthesised by Pfizer, that has been shown to block the pro-inflammatory effects of CRH [100,201,202] and also block mast cell activation in response to acute stress [199]. Similar agents could have therapeutic potential in IC, the symptoms of which often worsen stress, except that they cross the blood-brain-barrier (BBB) and could have unwanted adverse effects.

10.2 Astressin

Astressin (Neurocrine) is a more recent peptide receptor antagonist that has also been shown to block the peripheral effects of CRH, such as stress-related alterations in colonic motor function [203]. Such agents may potentially be more appropriate to use in IC because they do not cross the BBB. However, one problem with peptide receptor antagonists is that they may act as partial agonists for mast cell secretion [200].

10.3 Histamine-3 (H_3) receptor agonists

This is a new class of agents that act on presynaptic H_3-receptors, the activation of which leads to inhibition of synthesis and release of histamine [204] but also of a number of other neurotransmitters, such as serotonin and noradrenaline [205]. H_3-receptor agonists have also been reported to inhibit neurogenic vascular leakage in the airways [206]. Histamine was shown to inhibit TNF-α release from rat peritoneal mast cells [207] and serotonin release from porcine small intestine [208] through H_3-receptors. H_3-receptor agonists were also shown to inhibit brain mast cells [209] and it was further shown that their inhibitory effect may be through their action on sensory nerve endings found in close contact with mast cells [210]. The possible therapeutic significance of H_3-receptor agonists has been reviewed recently [211].

It is important to note that the new H_3-receptor agonist prodrug BP-2-94 has shown analgesic and anti-inflammatory properties [212]. With respect to IC, this agent reduced cyclophosphamide-induced cystitis in mice and significantly decreased leukocyte infiltration and protein extravasation in the urinary bladder [212].

10.4 Tizanidine (Zanaflex™)

Clonidine is an α_2-receptor agonist used to treat hypertension [31]. These catecholamine receptors are presynaptic and their activation leads to autoinhibition of synthesis/release of catecholamines [31]. Intrathecal clonidine added to sufentanil plus bupivacaine was shown also to produce longer duration of analgesia during labour. Moreover, clonidine administered intra-articularly after knee arthroscopy, improved pain relief in conjunction with morphine. The nociceptive effect of clonidine was determined to be at the level of the spinal dorsal horn of splanchnic neurons [213]. A recent study, however, showed that oral clonidine premedication did not change the efficacy of epidural anaesthesia.

Clonidine can cause depression and impotence. Clonidine may also trigger mast cell secretion [214], raising the possibility that it may be inappropriate for use in IC patients with documented bladder mastocytosis and/or history of allergic problems. The same may hold true for other newer agents (discussed below).

Tizanidine hydrochloride (zanaflex™) is a newer central α_2-adrenergic agonist primarily used to treat spasticity [215]. In addition, tizanidine has been used for the management of chronic tension type headache [216] and trigeminal neuralgia. Moreover, tizanidine was shown to be more effective than morphine in alleviating neuropathic pain [217]. It may, therefore, be useful for the treatment of pain associated with IC.

11. Other

Nitric oxide (NO) is established as a vasodilator and neurotransmitter [218,219]. It has also been implicated in nociceptive processing in the spinal cord [220]. Bladder NO levels were reported to be 30 - 50 times higher in various types of cystitis, including IC, than in controls and were considered to reflect inflammation [221]. However, nitric oxide synthase (NOS) activity and cyclic guanosine monophosphate (cGMP) levels were decreased in the urine of IC patients [222]. It was, nevertheless, felt that oral L-arginine, the substrate for NOS, could increase cGMP levels.

11.1 L-Arginine

As a result, L-arginine (1500 mg po. daily) was given to a small select group of 10 patients for six months intrathecally, apparently decreased IC symptoms [223]. This treatment also increased NOS and its metabolites in the urine. However, a subsequent report on the use of L-arginine suggested that it was not effective in IC [224]. A recent double-blind, placebo-controlled randomised, cross-over trial was conducted with 2.4 g per day oral L-arginine in 16 patients with IC [225]. There was a small significant drop in the overall score of the IC patients, but there was not statistically significant difference from controls; the authors concluded that L-arginine could not be recommended for the treatment of IC, especially since three patients withdrew because of severe flushing and headaches [225].

The use of this amino acid may depend on the population of IC patients selected. For instance, NOS inhibitors increase mast cell secretion [199,226], suggesting that NO may confer some tonal inhibition on mast cell secretion. Consequently, increase in NO may inhibit mast cell secretion and be beneficial in that group of patients with increased bladder mast cells or mast cell activation. In fact, NO inhibits mast cell-induced inflammation [227].

11.2 Bacillus Calmette-Guerin (BCG)

BCG has been used with some success for the treatment of transitional carcinoma of the bladder. A prospective, randomised, double-blind placebo study used Mice strain BCG in 30 patients who received six weekly installations of BCG or control with a mean follow-up of six months. There was a 60% positive response rate compared to a 27% placebo response rate based on 'exit' questionnaires [228]. Adverse side effects were similar in both groups and were mainly irritative voiding symptoms. A subsequent publication from the same group of researchers followed up 9 of the original responders for 27 months and reported general improvement with 81% decrease in pelvic pain. Unfortunately, this was a very small group of patients with little information on other relevant parameters. A recent double-blind, cross-over study compared the efficacy of intravesical BCG to DMSO in 21 patients, 11 with classic and 10 with non-ulcer IC [229]. There was no demonstrable benefit with BCG treatment, while there was a significant urinary frequency decrease with DMSO in classic IC and substantial pain decrease with DMSO in both classic and non-ulcer IC [229].

The mechanism of action of BCG in IC, if in fact it exists, is unknown. It could involve a switch from Th2 to Th1 type responses. Th1 cells generally produce TNF-α and INF-γ probably involved in defence against viruses, that inhibit the development of Th_2 responses [230]. Instead, Th2 cells secrete IL-4 and IL-6, likely important against extracellular organisms and promote allergic inflammatory responses [230]. This switch could also involve mast cells. For instance, Japanese school children with positive tuberculin responses were associated with lower incidence of asthma [231], similarly, bladder exposure to BCG may lead to reduced activation of bladder mast cells. However, the risk of systemic tuberculosis may also limit the therapeutic usefulness of intravesical BCG.

11.3 Doxorubicin (Adriamycin™)

This antineoplastic agent has also been used in IC patients with Hunner's ulcer. Weekly treatments (50 mg doxorubicin in 50 ml normal saline) for six weeks followed by monthly installations were used with bladder 'dwell' times of 2 h [232]. Follow-up was short (only five weeks in two of the three patients) and further documentation of the efficacy of this regimen is required before it enters the therapeutic mainstream.

11.4 Octreotide (Sandostatin™)

This is an analogue of the hypothalamic tetradecapeptide somastatin which inhibits growth hormone and prolactin release from the pituitary [31]. Somatostatin has also been shown to inhibit release of various molecules from endocrine, exocrine and immune cells, it is most commonly used for tumours associated with the gastrointestinal tract, such as gastrinoma and carcinoid [31]. It has recently also been reported to have anti-inflammatory properties [233]. It may,

therefore, be more useful for patients with both IC and IBS or IBD. However, somatostatin has been reported to stimulate mast cell secretion [234] and should be used with caution or be avoided in patients with documented bladder mastocytosis and/or a history of allergies.

12. Expert opinion

The treatment of IC is frequently frustrating for both the patient and physician. Treatment is hampered by the lack of a clear understanding of disease pathophysiology, as well as assessment of disease severity and/or progression.

Despite its chronicity and its enigmatic aetiology, IC could be treatable. The treatment modalities are generally safe and could alleviate most symptoms. PPS is the only oral drug evaluated in randomised, double-blind, placebo-controlled studies that has consistently been shown to have substantial benefit in alleviating the symptoms of IC without the discomfort of intravesical therapy. Oral hydroxyzine, as well as amitriptyline, are useful as first line treatment options. PPS plus hydroxyzine are currently being evaluated in a prospective, double-blind, placebo-controlled, multi-centre trial. Most other drugs (**Table 1**) must await similar rigorous evaluation.

A new concept in the treatment of IC is that of multi-modality approach using two or more drugs. The different mechanisms of action of the drugs used allow them to act at different points in the suspected pathogenic pathways in the bladder. Patients with documented bladder mastocytosis (greater than 5 mast cells per high power field) especially with evidence of activation and/or a history of allergies, should best be treated with a combination of hydroxyzine and PPS. There is now a new over-the-counter (OTC) formulation of the surface protecting proteoglycan chondroitin sulphate together with the flavonoid quercetin, both of which have mast cell inhibitory activity (Algonot-Plus™). This product can be added at any time as it may have additional benefit; in fact, quercetin even improved chronic prostatitis as discussed earlier. Algonot-Plus™is a non-prescription patented soft gel formulation that uses chondroitin sulphate from shark cartilage together with quercetin from a Latin American plant source mixed in natural, organic olive seed oil from the island of Crete in Greece to increase absorption. There are other OTC preparations with similar natural compounds individually; unfortunately, these contain either ingredients from sources with possible adverse effects or other additives that are likely to worsen IC symptoms. For instance, the available chondroitin sulphate preparations in tablet form permit less than 4% to be absorbed and most use chondroitin sulphate from cow trachea with the potential risk of spongiform encephalopathy ('mad cow disease'). Moreover, a common source of quercetin is from faba beans, ingestion of which could cause haemolytic anaemia in those individuals (many of Mediterranean origin) who have glucose-6-phosphate dehydrogenase deficiency. Unfortunately, these facts are not available to the unsuspecting consumer.

The future availability of H_3-receptor agonists with analgesic, anti-inflammatory and neurolytic activity may offer new hope for IC and similar conditions with neuropathic pain.

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