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Alosetron

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Contents

Abstract

▲ Alosetron is a potent and highly selective serotonin 5-HT_3 receptor antagonist which has been evaluated for the management of irritable bowel syndrome (IBS). It blocked the fast $5HT_3$-mediated depolarisation of guinea-pig myenteric and submucosal neurons *in vitro*, with half-maximal inhibition at approximately 55 nmol/L.

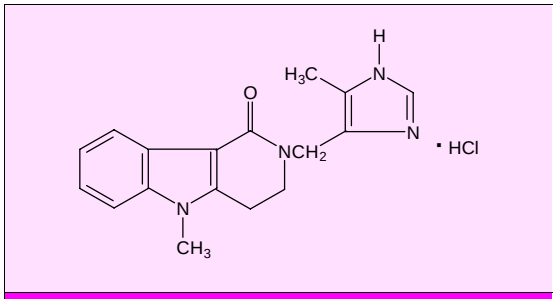
▲ Alosetron attenuated the visceral nociceptive effect of rectal distension in conscious or anaesthetised dogs. It increased the compliance of the colon to distension in patients with IBS and delayed colonic transit in patients with IBS or carcinoid diarrhoea and in healthy volunteers.

▲ A single dose of alosetron 4mg increased *in vivo* fluid absorption in normal human small intestine.

▲ In clinical trials in patients with IBS, alosetron 1mg twice daily was effective in relieving abdominal pain and discomfort. Alosetron was most effective in female patients and particularly in those with diarrhoea-predominant IBS.

▲ In patients with IBS and healthy volunteers who received alosetron, the most common adverse event was constipation.

Features and properties of alosetron (GR 68755)	
Indication	
Management of irritable bowel syndrome	Phase III; submitted for regulatory approval in Europe and other countries worldwide; approved and launched in the US
Mechanism of action	Serotonin 5-HT_3 receptor antagonist
Dosage and administration	
Usual dosage in clinical trials	2 mg/day
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetics (2mg oral dose)	
Peak plasma concentration	8.6 μg/L (6.1 μg/L for 1mg twice daily)
Time to peak plasma concentration	1.8h
Oral bioavailability (2 or 4mg oral dose)	50-60%
Elimination half-life	1.5h
Adverse events	
Most frequent	Constipation



Alosetron

Irritable bowel syndrome (IBS) is a common disorder thought to result from dysregulation of intestinal motor, sensory and CNS function. The characteristic symptoms of abdominal pain, bloating and disturbed bowel function (diarrhoea or constipation or both alternating) are attributable to disturbed intestinal motility and enhanced visceral sensitivity.[1,2]

Alosetron is a potent and highly selective serotonin 5-HT_3 receptor antagonist[3,4] which has been evaluated for the management of irritable bowel syndrome (IBS). 5-HT_3 receptors have been shown to be involved in motor and sensory processes in the gastrointestinal tract.[5,6]

1. Pharmacodynamic Profile

• Alosetron (0.01 to 1.0 μmol/L) blocked the fast 5-HT_3-mediated depolarisation of impaled guinea-pig myenteric and submucosal neurons, with an IC_{50} (concentration causing half-maximal inhibition) of approximately 55 nmol/L. This effect was concentration-dependent. At high concentrations (1 μmol/L) alosetron inhibited the 5-HT_{1P}-mediated slow depolarisation of these neurons. In second order submucosal neurons, it also inhibited fast and slow excitatory postsynaptic potentials evoked by mucosal stimulation. This effect was not seen with granisetron or ondansetron.[7]

• Inhibition of serotonin-induced flare response (a model of 5-HT_3 receptor activity) by alosetron occurred in a dose-dependent manner in healthy male volunteers who participated in a double-blind, placebo-controlled, crossover trial.[8] 12 volunteers were randomised to receive single doses of oral alosetron 0.05, 0.25 or 1mg, or placebo; dorsal intradermal injections of serotonin 160μM were administered at intervals over the subsequent 12 hour period and the flare size measured to determine the effect of the drug on flare response.[8] The median duration of action was 10 hours with the 1mg dose.[8]

Effects on Visceral Perception

In Animals

• In cat and rat animal models, alosetron antagonised the stimulatory activity of 2-methyl-5-HT on 5-HT_3 receptors on vagal afferents in the left cardiac ventricle; alosetron was 3 to 10 times more potent and showed a longer duration of effect than ondansetron in the rat model.[9] Alosetron produced potent inhibition of the depressor response to colorectal distension in an anaesthetised rat model; the half-maximal inhibitory dose of granisetron was 3 μg/kg. The potency of alosetron in this model was 5 to 10 times that of ondansetron or granisetron.[9]

• Alosetron attenuated the changes in blood pressure which occur following rectal distension in dogs. This vasoactive model represents a model for visceral pain. Increases in blood pressure produced by rectal distension were decreased by approximately 70 to 80% compared with placebo ($p < 0.05$) in anaesthetised dogs administered 0.1 to 10 mg/kg intravenously or 0.1 to 1 μg/kg intracerebroventricularly or conscious dogs given 10 mg/kg intravenously or 1 μg/kg intracerebroventricularly.[10]

In Humans

• In a trial that included 22 evaluable patients with IBS, alosetron 0.25 or 4mg twice daily for 7 days increased the compliance of the colon to distension produced by a barostat bag. Compared with placebo, alosetron 0.25 and 4mg twice daily increased the median volume of the barostat bag at which the first sensation was perceived (by 61and 90ml, respectively; $p = 0.07$ and 0.028, respectively). The volume at which pain was perceived was also increased versus placebo(by 71 and 84ml, respectively; $p = 0.039$ and 0.017, respectively).[11]

• In healthy volunteers (n = 12) alosetron 1mg twice daily for 6 days did not significantly modify compliance of the gastric wall to distension or visceral perception of gastric distension compared with placebo.[12]

Effects on Gastrointestinal Motility and Absorption

The effects of alosetron on gastrointestinal motility and absorption in healthy volunteers and patients with IBS or carcinoid diarrhoea have been evaluated in double-blind, placebo-controlled studies.

• A single dose of alosetron 4mg increased fluid absorption under basal conditions in normal human small intestine (by 34%; p = 0.03), but did not promote absorption or reduce secretion in cholera toxin-induced hypersecretion. In this *in vivo* volunteer (n = 7) study, a 30cm segment of jejunum was isolated by 2 occluding balloons.[13]

• In patients with IBS (n = 12), alosetron 2mg twice daily for 8 days delayed colonic transit after a meal by prolonging left colonic transit (23 *vs* 12 hours with placebo; p = 0.006). Mean whole gut transit time (as measured by transit of radioopaque markers) was slightly increased with alosetron compared with placebo but this was not statistically significant (72 *vs* 59 hours; p = 0.13). Small bowel transit time was unaffected by alosetron.[14]

• Similar effects were seen in an ileal brake model in healthy volunteers (n = 12) given the same dosage of alosetron. Median whole gut and colonic transit times were delayed by approximately 8 to 9 hours ($p < 0.05$ *vs* placebo).[15] After a single dose of alosetron 4mg, orocaecal transit time in healthy volunteers (n = 20) was increased significantly (310 *vs* 235 minutes; p value not stated).[16]

• In patients with carcinoid diarrhoea (n = 26), alosetron 0.5 or 2mg twice daily for 3 weeks significantly slowed proximal colonic emptying [$p < 0.05$ *vs* 0.1mg twice daily (p values *vs* baseline not reported)] but had no effect on gastric emptying or small bowel transit time.[17]

• Alosetron 4mg twice daily for 7 days had no adverse effects on oesophageal motility or lower oesophageal sphincter pressure (n = 20)[18] or on small bowel motor patterns (as measured by prolonged small bowel manometry; n = 9)[19] in healthy volunteers.

2. Pharmacokinetics

Absorption

• In 24 male volunteers who received alosetron 2mg twice daily for 28 days, mean maximum plasma alosetron concentration (C_{max}) values were 8.6 μg/L on day 1 [in a time (t_{max}) of 1.8 hours] and 12.4 μg/L (t_{max} 1.7 hours) on day 28; corresponding area under the plasma concentration-time curve (AUC) values were 26.6 and 39.4 μg · h/L.[20]

• Alosetron does not accumulate in the plasma during repeated oral administration of 1mg twice daily.[21] In a study conducted in 30 healthy male and female volunteers who received oral alosetron 1mg twice daily for 29 days, steady-state plasma concentrations of alosetron were reached on day 1. There was no evidence of accumulation of alosetron in the plasma on days 8, 15, 22 or 29; respective C_{max} values at these time-points were 6.1, 6.1, 5.9 and 6.1 μg/L, compared with 5.1 μg/L on day 1.[21]

• A single 4mg dose of alosetron produced a C_{max} of approximately 20 μg/L within 1.5 hours in healthy volunteers (n = 2).[22] The oral bioavailability was 47% after a 4mg dose in volunteers (number not reported)[23] and approximately 60% after a 2mg dose in 48 volunteers.[24]

• In 20 healthy volunteers, single-dose administration of alosetron 4mg with a high fat meal resulted in small but statistically significant decreases in C_{max} and AUC values and a slight increase in t_{max} (15 minutes) compared with fasted-state values.[25] However, the investigators concluded that these changes were unlikely to be of clinical significance.

Metabolism and Elimination

• Alosetron is cleared by metabolism and eliminated mainly by the kidney (approximately 70%), mostly as 12 metabolites, with only 6% of the total dose recovered as nonmetabolised drug. Since 1% is recovered in faeces as nonmetabolised drug, 93% of the dose is metabolised. The plasma elimination half-life ($t_{1/2}$) was approximately 1.5 hours for the parent compound and 3.0 hours for the parent compound plus circulating metabolites.[22] In 24 male volunteers, the $t_{1/2}$ was 1.4 hours. Oral clearance was 71 L/h.[26]

• Moderately higher systemic alosetron exposure was observed in female volunteers compared with males, as a result of lower systemic clearance. However, this was considered clinically insignificant by investigators who studied the pharmacokinetics of single doses of alosetron 2mg administered by intravenous infusion or orally in 12 healthy young male and 12 healthy young female volunteers.[27]

• Microbial *in vitro* biotransformation studies showed that alosetron was metabolised by N-demethylation of the indole group, hydroxylation at C4 of the lactam ring, dealkylation of the lactam nitrogen and extensive oxidative and reductive metabolism of the imidazole moiety.[28]

Influence of Age on Pharmacokinetics

• AUC and C_{max} values were higher in elderly female (n = 12) than in elderly male volunteers (n = 12) [62.4 *vs* 39.1 μg · h/L and 18.7 *vs* 11.6 μg/L, respectively, after a 2mg dose of alosetron]. Lower values for these parameters were found in young male volunteers (n = 24; 26.6 μg · h/L and 8.6 μg/L). C_{max} and AUC were increased on day 28 of twice daily administration in the young men (to 39.4 μg · h/L and 12.4 μg/L; p value not stated) but not appreciably in the other 2 groups. Ages of volunteers were not stated.[20] These results are consistent with those of a similar study reviewed by Gunput.[24]

Drug Interactions

• Alosetron did not significantly alter the metabolism or plasma concentrations of coadministered cisapride.[29] Coadministration of alosetron and theophylline did not alter the metabolism of theophylline by cytochrome P450 (CYP) 1A2.[30] In healthy female volunteers receiving an estrogen/progesterone-containing monophasic oral contraceptive, coadministration of alosetron 1mg twice daily resulted in small but statistically significant decreases in plasma levonorgestrel and ethinyl estradiol concentrations. Nevertheless, these decreases were not considered large enough to result in a clinically significant effect on the efficacy of the oral contraceptive.[31]

3. Therapeutic Trials

Alosetron has been evaluated in randomised, double-blind, placebo-controlled clinical trials in patients with IBS. After a 2-week screening period, treatment was given for 12 weeks. Double-blind, randomised trials that compared alosetron with placebo or mebeverine have been published.[32-34] Adequate relief of pain and discomfort[35] was used as a clinical end-point to evaluate the response to treatment in some studies. Other end-points included improvements in bowel function, sense of urgency, stool frequency and stool consistency.

• A randomised, multinational, dose-ranging study compared alosetron 0.1, 0.5 and 2mg twice daily with placebo in 454 patients with IBS. 63% of those treated with alosetron 2mg twice daily reported improvement of abdominal pain/discomfort ($p < 0.05$ *vs* placebo), compared with 51% of those who received placebo (fig. 1). Alosetron 2mg twice daily was most effective in those with firm to loose/watery stools. At this dosage, alosetron also significantly increased the median number of pain-free days compared with placebo during weeks 5 to 8 (to 36 *vs* 29; $p < 0.05$) and weeks 9 to 12 (to 41 *vs* 32; $p < 0.05$).[32]

• Alosetron was effective in relieving abdominal pain and improving bowel functions in non-constipated female patients with IBS.[33] This

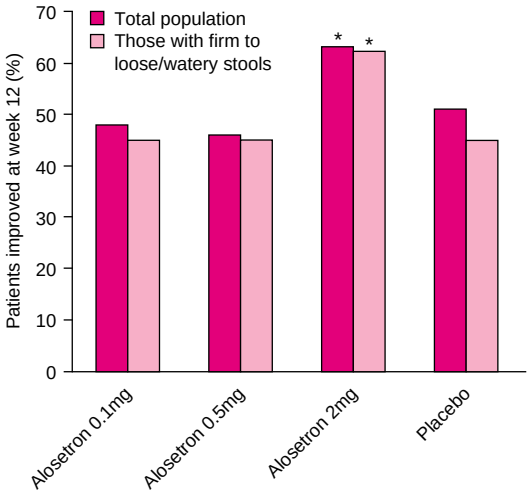


Fig. 1. Efficacy of alosetron in patients with irritable bowel syndrome (IBS). Proportion of patients reporting improvement of abdominal pain/discomfort. 454 patients were randomised to receive alosetron 0.1 (n = 113), 0.5 (111) or 2mg (113) twice daily or placebo (117) for 12 weeks in this multinational multicentre study.[32]
* $p < 0.05$ versus placebo.

double-blind, international, dose-ranging study randomised 370 male and female patients to receive alosetron 1, 2, 4 or 8mg twice daily or placebo. Among female patients, a significantly greater proportion of those receiving alosetron 1 or 2 mg twice daily reported adequate relief of their symptoms compared with placebo recipients (60 and 59 *vs* 33%; $p < 0.05$) [fig. 2]. Stool urgency, frequency and consistency significantly improved in female alosetron recipients. In male patients, alosetron did not appear to improve symptoms, with only stool consistency being improved versus placebo.[33]

• Similarly, alosetron 1mg twice daily was superior to placebo in relieving pain and discomfort [62 *vs* 42% at 12 weeks (estimated from graph); $p < 0.005$] and improving bowel function (urgency, consistency and frequency; $p \leq 0.001$) in a randomised, double-blind US study in 647 nonconstipated female patients with IBS.[36] The efficacy of the drug was apparent after the first week of treatment. Following cessation of treatment with alosetron, symptoms returned.

• In another double-blind, multicentre trial, alosetron 1mg twice day (n = 309) was also significantly more effective than placebo (n = 317) in relieving pain and bowel-related symptoms in nonconstipated female patients with IBS.[37] Significant relief of pain and discomfort versus placebo was documented 4 weeks after the start of treatment ($p \leq 0.05$) and was sustained for the remaining 8-week treatment period (i.e. 12-week total treatment period). Decreased urgency and frequency and firmer stools were reported 1 week after the start of treatment with alosetron. Relief of symptoms rapidly reverted following cessation of alosetron treatment, thus indicating that the effect seen in the patients was due to the drug and not a placebo effect.

• Alosetron was significantly more effective than mebeverine in the treatment of female nonconstipated patients with irritable bowel syndrome. Patients were randomised to receive alosetron 1mg twice daily (n = 319) or mebeverine 135mg 3 times daily (n = 304) for 12 weeks, followed by a 4-week treatment-free period.[34] Percentages of patients experiencing adequate relief of pain and discomfort were significantly higher in the alosetron treatment group than in the mebeverine group (56 *vs* 43% at week 8; $p < 0.001$: 58 *vs* 48% at week 12; $p = 0.009$).

• Compared with recipients of mebeverine, alosetron-treated patients had significantly lower proportions of days with urgency (38 *vs* 48%; $p < 0.05$) and mean stool frequency (2 *vs* 2.5%; $p < 0.01$). In addition, within 1 week of starting treatment, patients in the alosetron group had significantly firmer stools than the mebeverine-treated patients ($p < 0.001$).[34]

• Health-related quality of life (QOL) and productivity significantly improved in 324 female patients with diarrhoea-predominant IBS treated with alosetron 1mg twice daily in a placebo-controlled trial.[38] Eight of 9 IBS QOL scales significantly improved in the recipients of alosetron com-

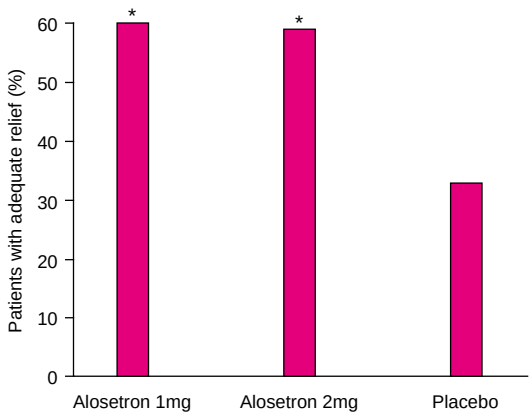


Fig. 2. Efficacy of alosetron in female patients with irritable bowel syndrome (IBS). Proportion of nonconstipated female patients who reported adequate relief of abdominal pain and discomfort (intention-to-treat data). 370 male and female patients were randomised to receive alosetron 1 (n = 72), 2 (n = 74), 4 (n = 76) or 8mg (n = 68) twice daily or placebo (n = 80) in this double-blind international study.[33] * $p < 0.05$ versus placebo.

pared with placebo ($p \leq 0.05$). In addition, alosetron produced significant improvements versus placebo in 6 of 9 MOS Short Form (SF)-36 scales in the diarrhoea-predominant population.

- In contrast, no significant improvements (versus placebo) in IBS QOL scales were reported in alosetron-treated female patients with alternating constipation/diarrhoea who also participated in the study; a significant improvement in 1 of 9 SF-36 scales was documented in these patients.[38]

- Health-related QOL also improved significantly in female patients with IBS treated with alosetron 1mg twice daily (n = 309) versus placebo (317) in another trial (intention-to-treat population).[39] Significant improvements in 8 of 9 IBS QOL scales ($p \leq 0.05$) occurred in the alosetron-treated patients. Alosetron recipients also experienced significant improvements versus placebo ($p \leq 0.05$) in bodily pain and vitality scales and in the Health transition item of the MOS SF-36 scale.[39]

4. Tolerability

- In an international study in which 370 male and female patients received alosetron 1, 2, 4 or 8mg twice daily or placebo for 12 weeks, the only adverse event of note was constipation. This was reported by 20% of those treated with alosetron 1mg twice daily to 29% of those who received 8mg twice daily.[33] Constipation was reported by 26% of patients receiving alosetron 1mg twice daily and by 7% of recipients of placebo in another trial.[37]

- The overall incidence of adverse events was similar among patients with IBS who received alosetron 0.1mg, alosetron 0.5mg, alosetron 2mg (each given twice daily) or placebo in a randomised, double-blind trial (section 3).[32] However, the incidence of constipation was significantly higher in patients treated with alosetron 0.5 or 2mg twice daily (13 and 17%, respectively) than in placebo recipients (3%) [p value not reported]. Alosetron treatment was not associated with any changes in laboratory values.[32]

- Adverse events were reported in similar proportions of nonconstipated female patients treated with alosetron 1mg twice daily (n = 318) or mebeverine 135mg 3 times daily (304);[34] 69 and 64% of alosetron and mebeverine patients experienced at least 1 adverse event; constipation was reported by 22% and 3% of alosetron and mebeverine recipients, respectively.

- In healthy volunteers who received alosetron 4mg twice daily, the most common adverse effect was constipation.[18] Other events included headache, anorexia, nausea, dizziness, loose stools (with 4mg single doses),[13] and abdominal cramping and flatulence/abdominal discomfort in volunteers who received alosetron 1mg twice daily.[12]

5. Alosetron: Current Status

Alosetron is a potent and highly selective 5-HT_3 receptor antagonist which is in late phase multinational studies. The drug has shown clinical efficacy in female patients with IBS and has been submitted for regulatory approval. The drug has recently been approved in the US for the treatment of female pa-

tients with IBS. Alosetron appears to be well tolerated.

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