mucus in stool, bloating, passage of gas) and stool parameters were recorded on a daily basis and assessed each week for 4 weeks (run-in, treatment and post-treatment periods). The hospital anxiety and depression scale (HADS) was observed each week by questionnaire before treatment. Results: The average age of all subjects was 42.3±2.9 years. The proportion of male was 36% (28/72). There was no difference between the two groups in demographic characteristics and HADS scores. The proportion of the patients who reported ‘moderate or more severe improvement’ (SGA≥3) to SGA was significantly higher in the placebo group than in the placebo group throughout the 2-week period of treatment and a week of post-treatment period (40.0% vs. 13.2% in the first week of treatment, 54.3% vs. 34.4% in the second week of treatment and 37.1% vs. 15.6% in the post-treatment week, p<0.05). The incidence of transient symptom scores and stool consistency improved significantly after treatment in the phloroglucinol group, but the improvements were not superior than those in the placebo group. The stool frequency decreased significantly in the phloroglucinol group compared to the placebo group (p<0.05). Conclusion: The phloroglucinol was effective on relief of overall IBS symptoms as well as improvement of stool frequency in patients with D-IBS.

Mo1323

Prucalopride for Constipation in a Tertiary Care Setting: Real Life Experience
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Introduction: Prucalopride is licensed for use in women with chronic constipation refractory to laxatives and has been used in the Durham Constipation Clinic since April 2010. The patient population attending the clinic represents the most severe end of the spectrum, with a high symptom burden and low quality of life. Local drug approval guidelines require that patients are monitored to assess safety and efficacy. Methods: Between April-Sept 2010, 90 patients receiving prucalopride with functional constipation were recruited with Prucalopride. Patients were asked to complete a questionnaire to assess efficacy and tolerability. Ethical approval is in place to store and analyse data. Results: 76 (84%) patients completed questionnaires and data presented is of these. Mean age 45yrs (range 19-77). Median duration of symptoms 18yrs (quart. 8-28). 39 (51%) patients were tertiary referrals. 60 (79%) had failed treatment with nurse-led therapies (biofeedback and/or rectal irrigation); 34 (45%) had failed treatment with surgical therapies. Mean duration of treatment was 12 weeks. 29 (38%) patients reported beneficial effects and were continuing to take the treatment. In these patients the following symptoms were improved: frequency of bowel movements (79%), complete emptying (59%), pain (62%), bloating (72%), straining (79%) and reduction/cramping of laxatives (59%). 63 (83%) patients suffered side effects, though most were mild and transient. Main side effects were: nausea (58% of patients), headaches (50%), pain (45%), diarrhoea (30%) and palpitations (17%). 202(26%) patients said they stopped treatment because of side effects, though 15 of these also reported absence of therapeutic effect at the time. 24 (32%) patients stopped treatment due to inadequate therapeutic effect, most making a decision to stop treatment themselves. 3 patients stopped treatment because of concomitant illness. Conclusion: The patients studied have failed a range of treatments provided by a tertiary centre and may represent a more refractory group. Despite this, a significant proportion of patients have responded to treatment with Prucalopride. Long term efficacy needs to be established. The frequency of early side effects is high, though most are mild and transient. If confirmed, this may have implications for monitoring and support of patients on initiation of treatment.

Mo1324

Molecular Pharmacology of Naronapride, a Selective 5-HT4 Receptor Agonist for the treatment of Constipation: Comparison With Other Prokinetic 5-HT4 Receptor Agonists
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In vitro receptor binding profiles of naronapride and its major metabolite, AT1-7500, were compared with those of other prokinetic 5-HT4 receptor agonists to assess the potential for receptor binding profiles of naronapride and its major metabolite, ATI-7500, were In Vitro for the Treatment of Constipation: Comparison With Other Prokinetic 5-HT4 Receptor Agonists. Compared with effective free drug/metabolite concentrations in plasma (Cp,f) to predict results showing >50% inhibition of ligand binding by 10 μM test article were considered to represent significant effects. Naronapride had high affinity for the 5-HT4 receptor (Ki= 2 μM) and dopamine D2 (Ki= 1.4 μM) receptors. Estimated effective free plasma concentrations of naronapride, cisapride, and tegaserod: Binding to molecular targets comprising a diverse spectrum of receptors, ion channels and transporters was measured in standard radioligand binding assays. Under the conditions of these studies, results showing >50% inhibition of ligand binding by 10 μM test article were considered to represent significant effects. Naronapride had high affinity for the 5-HT4 receptor (Ki= 1.4 nM). Of the remaining 63 targets, naronapride had measurable affinity for the 5-HT transporter (Ki=1.4 μM) and dopamine D2 (Ki= 61-269 nM), dopamine D3 (Ki= 269 nM), 5-HT1A (Ki= 1.3 μM), 5-HT2A (Ki= 0.9 μM), 5-HT2C (Ki= 1.7 μM), 5-HT3 (Ki= 0.8 μM), 5-HT4 (Ki= 1.3 μM), muscarinic M1 (Ki= 0.6 μM), M2 (Ki= 2 μM) receptors. Estimated effective free plasma concentrations of naronapride were <0.01 of the Ki values for all but 5-HT4 (Cp,f/Ki = 2.5) and D2 receptors (Cp,f/Ki = 0.01-0.06). The major metabolite of naronapride, AT1-7500, had no measurable affinity for any but 5-HT2B (Ki= 19.6-6.8 μM) and D2 receptors (Ki=13.9 μM). The AT1-7500 Cp,f/Ki ratios were <0.02. Tegaserod (100 μM) significantly inhibited radioligand binding to adrenergic (α1, α2, β1, β2), benzodiazepine, dopamine (D1, D2, D3, D4, D5), NMDA, histamine (H2), imidazoline (11, 12), melanotropin (MT1), muscarinic (M1, M2), neuromedin (NK1, NK2), opiate (kappa, mu), serotonin (5-HT1A, 5-HT1D, 5-HT2A, 5-HT2C, 5-HT4C), 5-HT5A, 5-HT5D and sigma receptors in L-type calcium channels (site 2) and transporters (NET, DA, choline, HITT). Inhibition constants determined for selected targets were: 5-HT1B= 2.9 μM, 5-HT1D= 48 μM, 5-HT2A= 110 μM, 5-HT2C= 21 μM. Although tegaserod Cp,f/Ki ratios do not predict off-target interactions In Vivo, radioligand assays have been linked to possible 5-HT4 receptor interactions by tegaserod and at least one of its metabolites. Ki values for cisapride binding were determined for selected serotonin receptors and ion channels only and showed significant binding at 5-HT2A (Ki = 9.0 μM), 5-HT2B (Ki = 74.110 μM), 5-HT3 (Ki = 1.3 μM). L-type calcium channels (Ki=797-510 nM) and sodium channels (site 2, 3K=50 nM), the cisapride metabolite, norcisapride had moderately high affinity for 5-HT3 receptors (Ki = 150 nM). Cp,f/Ki ratios for cisapride predicted potential off-target interactions In Vivo. The significance of these findings relative to potential off-target activities of new generation 5-HT4 receptor agonists and their metabolites will be discussed.