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A preliminary evaluation of comparative effectiveness of riluzole in therapeutic regimen for irritable bowel syndrome

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PEER REVIEW

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Comments

This is a prudent study which meticulously evaluates the action of riluzole on brain-gut axis in abating visceral hypersensitivity, using valid clinical scales and adequate statistical measures. Results are encouraging and exciting and may act as a lead to future therapies.

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ABSTRACT

Objective: To develop agents that are specifically effective in controlling the key disturbance of visceral hyperalgesia besides abating of associated multiple symptoms, and evaluate comparative effectiveness for IBS symptom relief for standard regimen (antispasmodic and probiotic) and add-on amitriptyine or riluzole regimens following two weeks administration.

Methods: 108 patients with visceral hypersensitivity accompanying IBS, divided into three groups were studied. First group received standard treatment (mebeverine 200 mg twice daily and probiotic 200 mg twice daily). Second group received add-on amitriptyline 25 mg before bedtime, while the third group got add-on riluzole 50 mg twice daily. Overall gastrointestinal symptom rating scale improving symptoms and hospital anxiety depression scale improving associated psychological morbidity were employed as measures at induction and at two-week follow-up period. Individual symptom scores were also examined to define the outcome profiles.

Results: Riluzole regimen resulted in significant reduction of overall gastrointestinal symptom rating scale score, not the other two regimens. Pain relief was seen with both riluzole and amitriptyline regimens significantly superior to standard treatment regimen, but riluzole effect appeared specific and independent anxiolytic effect. Amitriptyline caused relief in diarrhea and did not benefit in constipation point to non-specific remedial role in IBS.

Conclusions: Riluzole specifically relieves visceral hypersensitivity and is proved to be superior to current treatments in IBS patients. It appears a lead remedy based on glutamate transporter mechanisms in visceral hypersensititvity.

KEYWORDS

Visceral pain, Riluzole, Glutamate transporter, Irritable bowel syndrome

1. Introduction

While irritable bowel syndrome (IBS) is common in the West, early studies suggest that the prevalence of IBS is low in developing countries. However, recent studies point out that there was increasing prevalence of IBS in newly developing Asian countries. Together with the changes with evolution of Asian countries such as westernization of the diet and increased psychosocial stress, it is proposed that loss of internal protective effect, could give rise to a more uniform worldwide prevalence of IBS. IBS is one of the commonest gastrointestinal disorders. It is worrisome chronic disease of very productive life posing serious burden to medical care costs. The quality of life also suffers serious beating from IBS[1,2]. Varying systemic involvement of the gastrointestinal tract and both peripheral and central nervous system makes the syndrome difficult to be improved with single therapeutic agent[3,4]. Visceral hypersensitivity is highly prevalent in

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all functional bowel disorders with wider somatic referral of symptoms. Hypersensitivity at the level of the dorsal horn of the spinal cord is induced by peripheral inflammation or injury in the brain-gut axis. This process is mediated by mutual stimulation of N-methyl-d-aspartate receptors and neurokinin 1 receptors[5]. Tricyclic antidepressants (amitriptyline) have been used with variable success in control of IBS symptoms[6]. They cause sodium channel block in nociceptive neurons in an use-dependent manner. The antispasmodic compound mebeverine, a methoxybenzamine derivative is also widely used in IBS management[7]. It is thought to decrease motility and intraluminal bowel pressure via a direct effect on smooth muscle cells[8]. Probiotics also have shown some potential for global relief of IBS symptoms[9].

Neurotransmitter antagonist to reduce visceral hypersensitivity is an exciting new era for the treatment of functional gastrointestinal disorders[10]. The n-methyl d-aspartate (NMDA) receptor appears to be the most important molecular factor in the development of central sensitization at the spinal dorsal horn[11]. Changes in expression and glutamate uptake activity of spinal glutamate transporter are suspected to play a critical role in both induction and maintenance of hyperalgesic state by regulation of regional glutamate homeostasis. Human pharmacological studies have demonstrated that antagonism of the NMDA receptor preventing the development of central sensitisation within the oesophagus and ketamine may even reverse established visceral hypersensitivity[12]. Riluzole (a glutamate reuptake enhancer and NMDA receptor antagonist) was reported to attenuate hyperalgesia in neuropathic pain models at doses devoid of side effects, an action chiefly connected to the activation in glutamate reuptake[13]. The inclusion of riluzole in therapeutic regimen excluding amitriptyline is herein assessed for comparative effectiveness in relieving symptoms and improving quality of life in patients of IBS.

2. Materials and methods

2.1. Patients

After prior approval of institutional ethics committee, IBS patients aged 18 years or older with symptoms that fulfilled the Rome II criteria[14] for IBS for at least 6 months were included in the study. History, physical examinations (including sigmoidoscopy/colonoscopy), routine and special laboratory investigations were recorded. Patients were excluded if they were lactose intolerant or had any other significant medical condition requiring concurrent therapy. Cases with psychiatric disorder or substance abuse within the previous 2 years, pregnant or breast-feeding women and those using hormonal contraception were also excluded. All included cases were advised to observe week long drug free period prior to inclusion in the study.

2.2. Study design

Strictly in sequence, cases entering the study were prescribed A, B or C therapy regimens. Regimen A: mebeverine 200 mg twice daily and probiotic 200 mg twice daily; Regimen B: Regimen A+amytriptyline 25 mg before bedtime; Regimen C: Regimen A+riluzole 50 mg twice daily.

2.3. Clinical scales

Standard gastrointestinal symptom rating scale (GSRS)[15] was used as measure. Concurrent psychological morbidity was assessed using hospital anxiety depression scale (HADS)[16]. The scores were compared at induction and at 2 weeks of compliant adherence to the prescribed therapy. Non-compliance with the prescribed regimen was thoroughly enquired and cases with more than one occasion of missing medicine were excluded.

2.4. Statistical methods

Overall variance of outcomes relating different symptoms in the compared regimens was examined using Kruskal-Wallis ANOVA test[17]. Chi square statistic was employed to evaluate relative outcomes of symptom relief in the compared treatment groups. P value less than 0.05 was considered significant. Interrelation among different symptoms was analysed using Spearman's correlation coefficient (Q)[18]. SPSS version 17 software was used.

3. Results

Table 1 summarizes GSRS scores prevalent among the overall studied sample of IBS patients. Pain was constantly present in all cases. Indigestion also occurred in majority,

Table 1
Overall profile of GSRS scores.

	Number of cases	GSRS score			Std. deviation	Variance	Mean	
		Range	Min.	Max.			Statistic	Std. error
Reflux	55	5	1	6	1.292	1.669	3.67	0.174
Pain	108	8	1	9	2.278	5.189	4.77	0.219
Indigestion	63	10	1	11	2.537	6.437	5.83	0.320
Diarrhoea	71	6	2	8	1.647	2.714	4.17	0.196
Constipation	19	6	2	8	1.968	3.871	4.74	0.451