The acid pocket, hiatal hernia and TLESRs: essential players in the pathogenesis of gastro-esophageal reflux disease

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The GABA$_B$ receptor agonist AZD9343 inhibits transient lower esophageal sphincter relaxations and acid reflux in healthy volunteers: a phase I trial

Submitted

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Abstract:

Introduction: Transient lower esophageal sphincter relaxations (TLESRs) are considered the main mechanism underlying gastroesophageal reflux both in healthy subjects and patients with reflux disease and therefore represent an interesting target for treatment. Baclofen, a GABA<sub>B</sub> receptor agonist, reduces the number of TLESRs and reflux episodes, but is not optimal for clinical application due to its central side effects. Therefore, new agents devoid of these side effects are required. In the present study, the effect of AZD9343, a new selective GABA<sub>B</sub> receptor agonist, was studied on meal-induced TLESRs and its safety profile was evaluated in healthy volunteers.

Methods: Twenty-seven healthy male subjects (19-47 yrs) were included in a placebo-controlled, randomized, two-centre phase I study. All subjects underwent esophageal manometry (10 channel water perfused sleeve assembly) and pH-metry during 3 hrs after ingestion of a solid meal. One and a half hour before meal ingestion, a single oral dose of placebo, 60 and 320 mg AZD9343 or 40 mg baclofen was given on 4 separate days at least 7 days apart. TLESRs and acid reflux episodes were identified according to previously published criteria (Holloway et al., 1995).

Results: 25 of the 27 studies were complete and suitable for analysis. Somnolence was the most commonly reported side effect after 320 mg AZD9343 and baclofen. Reversible short-lasting paresthesiae of mild intensity were reported after intake of 60 and 320 mg AZD9343. The highest dose of AZD9343 and baclofen significantly reduced the number of TLESRs in the postprandial period with an average of 32% (95% CI: 15-44%) and 40% (95% CI: 26-51%) respectively. Acid reflux episodes were also significantly reduced by both doses of AZD9343 and baclofen compared to placebo. Like baclofen, both doses of AZD9343 increased mean LES pressure before meal intake compared to placebo. Finally, 320 mg AZD9343 and baclofen significantly reduced the number of swallows compared to placebo (mean reduction of 22% (95% CI: 6-35%) and 35% (95% CI: 18-49%)) whereas 60 mg AZD9343 had no effect on swallowing.

Conclusions: Like baclofen, the selective GABA<sub>B</sub> receptor agonist AZD9343 dose-dependently reduces the number of TLESRs and acid reflux episodes, increases basal LES pressure and reduces swallowing. These findings extend the concept that GABA<sub>B</sub> agonists are potent reflux inhibitors. However, discovery of analogues with an improved side effect profile is warranted.
Introduction

Gastroesophageal reflux disease (GERD) is a common disease characterised by symptoms like heartburn, acid regurgitation and retrosternal pain, resulting from prolonged acid exposure of the esophageal mucosa. Symptoms are present in 30-40% of the Western population and about 5% suffer from daily symptoms. The disease has a profound impact on the quality of life of those affected and may give rise to complications such as esophagitis, Barrett’s esophagus, strictures and extra-esophageal manifestations such as asthma, chest pain and laryngitis. Acid suppression therapy has provided a very high healing rate of esophagitis and has increased symptom relief of GERD. However, there are still significant medical needs that remain unfulfilled, such as complete and fast symptom control. Moreover, additional control of the non-acid reflux component may be of clinical importance, as non-acid reflux can cause symptoms and, when bile acids are present, may lead to mucosal damage.

The lower esophageal sphincter (LES) plays a central role in regulating flow across the gastroesophageal junction by generating a tonic pressure to prevent reflux of gastric contents into the esophagus. Transient lower esophageal sphincter relaxations (TLESRs), occurring in the absence of a swallow, are the predominant mechanism underlying reflux, both acid and non-acid, in healthy volunteers and in GERD patients. Therefore, pharmacological inhibition of TLESRs is a potential target to treat GERD. To date the best studied pharmacological agents to reduce the rate of TLESRs are γ-aminobutyric acid type B (GABA₉) receptor agonists.

The selective GABA₉ receptor agonist baclofen, used in the treatment of spasticity, reduces the rate of TLESRs and the number of acid reflux episodes in normal subjects and in GERD patients. This effect most likely depends on inhibition of mechanosensitive gastric vagal afferents and their central synaptic connections with brain stem neurons, leading to a raised threshold for action potential firing and reduction of transmitter release, respectively. Furthermore, baclofen increases LES pressure and reduces the number of acid reflux episodes and symptoms of heartburn. However, the sedative effect of baclofen along with other central side effects precludes its use for general treatment of GERD.

The compound AZD9343 is a full agonist of the human GABA₉ receptor, and dose dependently inhibits the number of TLESRs in dogs, with a maximum of approximately 60%. In addition, the effect of AZD9343 on TLESRs remained unaltered during 14 days of treatment in dogs, suggesting the absence of tolerance development, an important feature when a drug may be given on a chronic basis. First tolerance studies in man with AZD9343 showed reversible and short-lasting paresthesiae at the highest dose levels, without any further significant clinical findings (unpublished results, data on file). The aim of this study was to evaluate the effect of single oral doses of AZD9343 on the occurrence of meal-induced TLESRs in healthy subjects, and to compare its effect with that of baclofen.
Materials and Methods

Subjects
Studies were performed in 27 healthy male subjects (19-47 yrs, median age 22). Subjects were free of any gastrointestinal symptoms, had no history of gastrointestinal surgery and did not take any medication known to influence gastrointestinal motility. Urine samples were taken prior to the study and at random once during the study to check for any recent drug abuse. Written informed consent was obtained from all subjects, and the study was approved by the Medical Ethical Committees of the Academic Medical Centre Amsterdam and the University Medical Centre Utrecht.

Study design
The effect of single oral doses of AZD9343 was evaluated in a randomized, double-blind, placebo controlled two-centre phase I pharmacodynamic study. In a four-period cross-over design subjects received two single oral doses of AZD9343 (60 mg and 320 mg), baclofen (40 mg) and placebo with subsequent combined esophageal manometry and pH metry. Each dose administration was separated by a washout period of at least seven days. Intake of alcohol and nicotine was not allowed 2 days and 24 hours prior to and during the study, respectively. The studies were performed after an overnight fast. A cannula was inserted into a forearm vein for blood sampling. The manometric and pH catheter were introduced through an anaesthetised nostril and positioned so that the sleeve straddled the LES. The pH electrode was located 5 cm above the proximal margin of the LES. All studies were performed in the sitting position. Recording started just after dosing and continued for 4.5 hours. In order to increase TLESRs, a standardised meal (700 kCal, 30% fat) was served, to be completed 1.5 hours post-dose, ie. the time point when peak plasma concentration of AZD9343 was expected to occur. After the meal, patients remained upright and manometric/pH recordings were obtained for three more hours. Subjects stayed in the clinic for at least 12 hours after drug administration and returned the next morning, 24 hours after drug administration, for blood sampling, blood pressure and pulse measurements. Adverse events were followed carefully throughout the study and subjects were monitored with regard to blood pressure and pulse at regular intervals. Blood samples were collected frequently during each study day for determination of AZD9343 and baclofen in plasma.

Recording methods
Esophageal manometry was performed using a 10-lumen silicone rubber assembly (Dentsleeve International Ltd, Mississauga, Ontario, Canada) with a 6 cm long reversed perfused sleeve sensor incorporated at its distal end to monitor LES pressure. Side holes monitored pressure in the stomach (3 cm below the distal margin of the sleeve), just at the proximal margin of the sleeve and at 4, 9, 14, 19 and 24 cm above the sleeve. Four pharyngeal side holes were available to monitor swallows, of which two were selected for this purpose. The side holes and the sleeve were perfused with degassed distilled water
at 0.2 ml min⁻¹, using a pneumohydraulic capillary perfusion pump (Dentsleeve Pty, Belair, South Australia) and hydraulic flow restrictors (Dentsleeve International Ltd, Mississauga, Ontario, Canada). The pharyngeal side hole was perfused with air at a rate of 0.8 ml min⁻¹ to reduce pharyngeal triggering of TLESRs. Pressures were sensed by external transducers connected to a polygraph (MMS, Enschede, the Netherlands and Medtronic Synectics, Järfälla, Sweden). To measure acid reflux, esophageal pH was recorded with an antimony electrode with built-in reference, positioned 5 cm above the proximal margin of the LES. Before and after the study the pH electrode was calibrated at 37 °C using pH 1.0 and 7.0 buffer solutions (Medtronic, Skovlunde, Denmark). Signals were digitalised, computer-processed, and stored on a personal computer for subsequent analysis. All signals were sampled at a frequency of 20 Hz.

**Data analysis**

Basal LES pressure was measured at end-expiration relative to intragastric pressure, and was determined as visual means of one-minute periods every 15 minutes, provided that the measurement was stable and no TLESR, swallow or slow drift occurred during the time period.

TLESRs were evaluated according to previously published criteria²²: 1) absence of swallowing for 4 seconds before to 2 seconds after the onset of LES relaxation, 2) relaxation rate of ≥ 1 mmHg s⁻¹, 3) time from onset to complete relaxation of ≤ 10 seconds, and 4) nadir pressure of ≤ 2 mmHg. LES relaxations associated with a swallow and fulfilling the above mentioned criteria 2, 3 and 4 that lasted more than 10 seconds were included as TLESR. TLESRs were counted for each subject during the preprandial period and the 3 postprandial hours. In addition, the number of TLESRs accompanied by an acid reflux episode was determined, as well as the total amount of acid reflux episodes and total acid exposure time.

Acid reflux episodes were defined as a decrease in esophageal pH below 4 for more than 5 seconds or, if basal esophageal pH was already below 4, as a further decrease in pH of at least 1 pH unit for more than 5 seconds. Concurrence of a TLESR and an acid reflux episode was defined as the drop in pH starting during the time of a TLESR.²³, ²⁴ The rate of spontaneous swallowing was determined by counting the pharyngeal pressure waves.

**Drugs**

The doses of AZD9343 administered in this study were selected on the basis of data collected during the first study in man. 320 mg was below the highest dose without any reported adverse event in this first study. All study medication was provided by AstraZeneca R&D Lund, Sweden. AZD9343 60 and 320 mg were administered as oral solutions, whereas baclofen (Lioresal ®) and placebo were administered as capsules. Blinding was ensured according to the double dummy principle: subjects received either AZD9343 (60 or 320 mg) oral solution and a placebo capsule, or a placebo oral solution and a baclofen capsule, or a placebo oral solution and a placebo capsule. For the safety of the subjects, the dose of AZD9343 60 mg always preceded the dose of AZD9343 320 mg. The higher dose of
AZD9343 was always given in the period immediately after the low dose to reduce the risk that period effect would confound treatment effect. Subjects were randomized in the same proportion to each of the six sequences of the four treatments that were allowed according to the study design.

**Plasma sampling and analysis**

Blood samples were taken from a forearm vein at multiple time points during each study day up to 24 hour after drug administration. After separation of plasma, samples were stored at -20 °C until analysis. The plasma concentration of AZD9343 was determined by Pharma Bio-Research Group B.V. (Assen, The Netherlands) using liquid chromatography and mass spectrometric detection. The plasma concentration of baclofen was determined by DMPK & Bioanalytical Chemistry AstraZeneca R&D (Mölndal, Sweden) using liquid chromatography and mass spectrometric detection. For each placebo treatment period, only 1 plasma sample around the expected C\text{max} was analysed to confirm that the subject had not been given AZD9343 or baclofen. For each baclofen treatment period, 1 plasma sample around the expected C\text{max} was analysed to confirm that the subject had been given baclofen.

**Statistical analysis**

The pharmacodynamic variables are presented as the mean ± S.E.M. Pair-wise comparisons of treatments were primarily made by calculating the individual differences in the number of TLESRs during the 3 hour postprandial period with calculating test-statistics and confidence intervals based on a normal distribution. The number of acid reflux episodes, time with esophageal pH < 4 and swallowing rate were compared pair-wise between the treatments and results are presented in terms of confidence intervals or means ± S.E.M, calculated in the same way as for the number of TLESRs. Data on basal LES pressure is presented descriptively. A P-value of < 0.05 was considered to be significant.

The pharmacokinetic variables, except for t\text{max}, were logarithmically transformed and results are presented in terms of geometric means with 95% confidence intervals. Values of t\text{max} are presented descriptively.

Sample size calculation was based on the number of TLESRs during the 3 hour postprandial period. With a sample size of 17, a two-sided 95% confidence interval for the difference between an active treatment and placebo would with 80% probability extend no more than 30% of the placebo mean from the observed difference. Twenty-four subjects were to be randomized in order to have at least 17 evaluable subjects. Finally, 27 subjects were enrolled in the study.

**Results**

Of the 27 randomized subjects, 1 subject failed to ingest the standardised meal. Another subject was excluded from analysis due to low to absent basal LES pressure. Consequently,
pharmacokinetic analysis was performed based on data from 26 subjects, whereas 25 subjects were evaluable in terms of manometric and pH recordings.

**Plasma levels**

Maximum AZD9343 plasma concentrations were reached at 1.75 (0.95-2.02) hours and 1.75 (1.50-2.00) hours after administration of AZD9343 60 and 320mg, respectively. C\text{max} was 2.2 (1.7-2.8) µmol L\text{–}¹ and 16.3 (12.3-21.6) µmol L\text{–}¹ for the low and high doses, respectively (Figure 1). Mean t½ was 5.6 (4.5-7.1) hours for AZD9343 60mg and 10.2 (7.9-13.3) hours for AZD9343 320mg. Plasma concentration in samples taken at 24 hours after administration of AZD9343 60mg was below the lower limit of quantification in all subjects, whereas all subjects had still measurable plasma levels 24 hours after administration of AZD9343 320mg.

![Figure 1. Plasma levels of AZD9343. Peak plasma concentrations occurred at 1.75 hours after dosing, i.e. during the first postprandial hour. Maximum plasma concentration in AZD9343 320mg was 7.5 times higher compared to AZD9343 60mg.](image)

**Side effects**

All reported side effects were of mild to moderate intensity. Somnolence was most commonly reported as side effect after 320mg AZD9343 (reported by 8 subjects) and baclofen (reported by 10 subjects). Furthermore, reversible, short-lasting paresthesiae were reported after intake of 60mg (2 subjects) and 320mg AZD9343 (9 subjects) but not after baclofen. Onset of paresthesiae started between 2-40 minutes and symptoms were resolved within 4-109 minutes. Furthermore, dizziness was reported after intake of baclofen (9 subjects) but to a lesser extent after intake of AZD9343 (reported by 3 subjects).

**TLESRs and reflux**

Before meal intake, 4.0 ± 0.9 TLESRs per 75 min were recorded during placebo. This was reduced to 3.0 ± 1.7, 1.6 ± 0.3 and 1.9 ± 0.3 TLESRs after AZD9343 60mg, 320mg and baclofen treatment, respectively (Figure 2).
Meal ingestion resulted in an increase of TLESRs. This increase was most pronounced in the 1st postprandial hour (placebo: 6.6 ± 0.5/hr) whereas in the 3rd hr, the number of TLESRs had returned to preprandial level (placebo: 2.9 ± 0.4/hr) (Figure 2). Treatment with the highest dose of AZD9343 and baclofen significantly reduced the meal-induced increase of TLESRs in the total postprandial period (placebo: 4.7 ± 0.3/hr; AZD9343 60mg: 3.9 ± 0.2/hr (ns); AZD9343 320mg: 3.6 ± 0.6/hr (P<0.05); baclofen: 2.7 ± 0.2/hr)(P<0.05) (Figure 3A). This corresponds to an inhibition of 16% (95% CI: -7-34%), 32% (95% CI: 15-45%) and 40% (95% CI: 26-51%) by AZD9343 60mg, 320mg and baclofen compared to placebo, respectively (Figure 3B). The reduction in TLESRs was most pronounced during the second postprandial hour (2nd hour: placebo: 4.7 ± 0.5/hr; AZD9343 60mg: 3.6 ± 0.3/hr; AZD9343 320mg: 2.6 ± 0.4/hr; baclofen: 2.2 ± 0.3/hr).

Before meal intake, hardly any acid reflux episodes occurred in all treatment groups. After meal intake the number of acid reflux episodes was increased to 8.9 ± 1.4 episodes/3hrs during placebo, most pronounced during the first postprandial hour. This increase in reflux episodes was significantly inhibited by both doses of AZD9343 and baclofen (AZD9343

**Figure 2.** Number of TLESRs per hour. Already before meal intake, a reduction in TLESRs was observed after AZD9343 320mg and baclofen, statistically significant only after AZD9343 320mg. Meal-induced increase in TLESRs was most pronounced during the first postprandial hour. However, analysed per postprandial hour no significance was observed. Data are represented as means ± SEM. * P<0.05 compared to placebo (paired Student’s t-test).

**Figure 3.** Effect of AZD9343 (60 and 320mg) and baclofen (40mg) on (A) the postprandial rate of TLESRs and (B) the percentage inhibition of TLESRs. Values are presented as means ± SEM. * P<0.05 compared to placebo (paired Student’s t-test).
60mg: 6.1 ± 0.9 episodes /3hrs; AZD9343 320mg: 2.8 ± 0.5 episodes /3hrs; baclofen: 3.8 ± 0.6 episodes /3hrs) (Figure 4A).

The percentage of acid reflux episodes related to a TLESR was 66% during placebo and did not differ after AZD9343 and baclofen treatment (AZD9343 60mg: 63%; AZD9343 320 mg: 66%; baclofen: 70%). On the other hand, the percentage of TLESRs accompanied by an acid reflux episode was significantly decreased after AZD9343 320mg compared to placebo (placebo: 40%; AZD9343 320 mg: 20%, p<0.0001), but not after AZD9343 60 mg and baclofen (AZD9343 60mg: 32%; baclofen: 30%).

**Time with esophageal pH < 4**

Before meal intake, the acid exposure time was negligible for all groups. After placebo, the postprandial percentage of time with pH < 4 in the esophagus was 3.8 ± 0.8%, mainly resulting from acid reflux occurring during the second and third postprandial hour. The acid exposure time was significantly reduced after AZD9343 320mg to 0.9 ± 0.2%. AZD9343 60mg and baclofen had no effect on time pH < 4 (AZD9343 60mg: 2.4 ± 0.5%; baclofen: 3.6 ± 0.7%) (Figure 4B). Furthermore, acid clearance time was not affected by any of the active treatments (data not shown).

**Basal LES pressure**

Before meal intake, basal LES pressure was 11.4 ± 1.1 mmHg during placebo. This was significantly increased after both doses of AZD9343 and baclofen (AZD9343 60mg: 15.5 ±
1.2 mmHg; AZD9343 320mg: 16.3 ± 1.7 mmHg; baclofen: 14.9 ± 1.5 mmHg). In all study groups, meal ingestion resulted in a reduction of LES pressure during the first postprandial hour, gradually returning towards preprandial levels. Although not significant, an increase in LES pressure was observed after AZD9343 (AZD9343 60mg: 12.7 ± 0.3 mmHg; AZD9343 320mg: 13.1 ± 0.5 mmHg) and baclofen (12.2 ± 0.4 mmHg) compared to placebo (11.0 ± 0.3 mmHg) during the total postprandial period, most pronounced during the second and third postprandial hour (Figure 5).

**Figure 5.** Effect of AZD9343 (60 and 320mg) and baclofen (40mg) on basal LES pressure. Values are represented by mean ± SEM. * P<0.05 for all active treatments compared to placebo (paired Student’s t-test). (See colour figures, page 158)

![Graph showing effect of AZD9343 and baclofen on LES pressure](image)

**Figure 6.** Effect of AZD9343 (60 and 320mg) and baclofen (40mg) on (A) total postprandial swallowing rate and (B) swallowing rate per hour. Values are depicted as mean ± SEM. * P<0.05 compared to placebo (paired Student’s t-test).

![Graph showing effect of AZD9343 and baclofen on swallowing rate](image)
Swallowing rate

During the pre meal period, swallowing rate was comparable between the groups (placebo: 104 ± 10 /75min; AZD9343 60mg: 109 ± 9 /75min; AZD9343 320mg: 83 ± 6 /75min; baclofen: 89 ± 7 /75min). After meal ingestion, 66 ± 4 swallows /hr were recorded during placebo. This was significantly reduced with 22% (95 CI%: 6-35%) to 47 ± 2 swallows /hr after AZD9343 320 mg and with 35% (95% CI: 18-49%) to 43 ± 3 swallows /hr after baclofen. No effect was observed after AZD9343 60mg (Figure 6).

Discussion

The GABA<sub>B</sub> receptor agonist baclofen, a potent inhibitor of TLESRs, has been extensively investigated in patients with GERD. Both in healthy subjects and patients with GERD, baclofen reduces esophageal acid exposure and diminishes reflux-associated symptoms. In contrast to acid suppressive agents, inhibitors of TLESRs reduce both the number of acid and non-acid reflux episodes and hence are referred to as reflux inhibitors. Although effective, treatment with baclofen induces central side effects such as sleepiness and dizziness, making it not optimal for wide clinical use. Therefore, the present study investigated the effect of a new GABA<sub>B</sub> agonist, AZD9343, and compared its activity to that of baclofen.

In the present study, we showed that AZD9343 dose-dependently reduced the number of TLESRs by up to 32%. The degree of inhibition was comparable to that of baclofen: in the present study, TLESRs were reduced by 40% whereas in previous studies a reduction of more than 60% after the same dose of baclofen was observed in healthy subjects. However, the study by Lee et al. was performed with a barostat bag placed in the proximal stomach and recordings were performed for only 2 instead of 3 postprandial hours. Our findings were more in accordance with previous studies performed in GERD patients, showing 33% to 40% reduction after baclofen 40 mg and identical study protocols. The reduction in TLESRs differed in time, i.e. the effect of both AZD9343 and baclofen was most pronounced in the second postprandial hour, whereas in the first and third hour, the reduction was rather small. This finding contrasts with previous studies where the inhibitory effect of baclofen on TLESRs was significant for all postprandial hours. One possible explanation for this discrepancy, at least for AZD9343, could be insufficient plasma levels. However, as shown in Figure 1, plasma levels peaked in the first postprandial hour. Moreover, we noticed a significant increase in LES pressure after AZD9343 intake, which was already present before meal intake. On the other hand, the dose of baclofen was similar as in previous studies. Therefore, insufficient plasma levels of AZD9343 or baclofen seems rather unlikely. The lack of a significant effect in the third postprandial hour could be explained by the low number of TLESRs. Three hours after meal intake, the stomach has most likely completely emptied removing the trigger for TLESRs. The lack of an effect during the first postprandial hour, however, remains unclear.

In line with the reduction in TLESRs, AZD9343 dose dependently reduced the number of acid reflux episodes with a maximum of 70%, with the highest dose also significantly
reducing acid exposure time. Baclofen, on the other hand, significantly reduced the number of acid reflux episodes (61%) but not acid exposure time. Acid exposure time not only relies on the number of reflux episodes but also on esophageal acid clearance and as a consequence, swallowing rate. In our study, however, the reduction in swallowing rate, both observed after AZD9343 and baclofen, was not accompanied by a change in acid clearance time. The lack of effect on acid exposure and acid clearance time after baclofen is comparable with previous studies in healthy subjects. This is most likely explained by the low level of acid exposure in healthy subjects even during placebo, making any inhibitory effect difficult to detect. On the other hand, Ciccaglione and Marzio showed a reduction in acid reflux episodes and esophageal acid exposure time in both healthy controls and GERD patients. However, in that study subjects were treated and measured for 24 hours. Variation in effect of baclofen on total acid exposure time has also been described in GERD patients, with a higher percentage acid exposure time. Probably, the high intra-subject variability in postprandial acid exposure contributes to these variations, and could also explain the differences observed in our study. Besides acid exposure time, the percentage of TLESRs associated with an acid reflux episode was also significantly decreased after intake of AZD9343 320mg, but not after baclofen. If true, these observations might be explained by an effect of the drug on either acid secretion or on emptying of the proximal stomach. However, animal studies have described a dual inhibitory and stimulatory effect of baclofen on acid secretion. Whether these effects are involved in the present study is unclear.

Overall, AZD9343 was well tolerated by all subjects with somnolence and reversible, short-lasting paresthesiae as most frequently reported side effects. The rapid onset, short duration and mild-to-moderate character of the paresthesiae were less in intensity compared to baclofen, but similar to previous observations in an earlier study in man with AZD9343 (data on file). Based on the reduction of swallowing and the presence of somnolence, AZD9343, like other GABA\textsubscript{B} receptor agonists, most likely crosses the blood-brain barrier to some extent. The increase in paresthesia after AZD9343 but not baclofen, and conversely, the increase in dizziness after baclofen but not AZD9343, clearly shows that there are as yet unexplained qualitative differences between the compounds.

At present, the treatment of choice for GERD is undoubtedly acid suppression; the success rate of endoscopic healing in esophagitis patients approximates 70-90%, symptom control is obtained in more than 70% of patients and above all, the safety profile is exceptionally good. Given these features, one may wonder if there is a need for new drugs to treat GERD. It should be emphasized though that acid suppression renders acid reflux episodes non-acid, but does not reduce the number of reflux episodes. Persistent symptoms during PPI treatment may therefore result from ongoing non-acid reflux and could benefit from reflux inhibitors such as GABA\textsubscript{B} agonists. A previous study showed that persistent bile reflux during PPI treatment was reduced by baclofen. In addition, persistent GERD symptoms were improved when baclofen was added to the PPI regimen. These data suggest that reflux inhibitors given as add-on treatment to patients with PPI resistant symptoms could be a major indication. Clearly, this implies that TLESRs should be a major mechanism of reflux in these patients. Especially in the presence of a large hiatal hernia, other mechanisms such
as strain-induced reflux or free reflux when LES pressure is low become more important.\(^8\), \(^34\), \(^35\) For example, acid trapped within the hiatal hernia will reflux during swallowing\(^36\), a phenomenon resistant to reflux inhibitors and potentially leading to reduced efficacy in this subgroup of patients. Furthermore, the exact role of hiatal hernia in the pathogenesis of excess reflux remains controversial in whether a hiatal hernia elicits the occurrence of TLESRs or not.\(^35\), \(^37\) On the other hand, the dual action on TLESR and basal LES pressure is unique and in some patients, perhaps the latter effect may be equally important to the effect on TLESR. Studies evaluating the efficacy of reflux inhibitors in patients with a hiatal hernia are therefore awaited, especially as most PPI resistant patients have a large hiatal hernia.\(^38\)-\(^40\)

In conclusion, the present study demonstrates that the GABA\(_B\) receptor agonist AZD9343 significantly inhibits the increase in TLESRs evoked by meal ingestion, increases basal LES pressure, reduces the number of acid reflux episodes and total acid exposure time, and reduces spontaneous swallowing. Comparable to baclofen, especially the highest dose of AZD9343 induced side effects, mainly somnolence and short lasting paresthesiae, making this drug less attractive for further clinical development. Nevertheless, the present data further confirm that the concept of GABA\(_B\) receptor stimulation is a very promising approach for treating GERD patients. New agents devoid of side effects and with a higher efficacy are, however, awaited.

## Reference List


