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The novel, peripherally restricted $GABA_B$ receptor agonist lesogaberan (AZD3355) inhibits acid reflux and reduces esophageal acid exposure as measured with 24-h pHmetry in dogs☆

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ABSTRACT

While patients with symptoms of gastroesophageal reflux disease generally respond well to proton pump inhibitors, 20–30% continue to experience troublesome symptoms. In such cases, agents that target transient lower esophageal sphincter (LES) relaxation may be useful as add-on therapy to proton pump inhibitors. The $GABA_B$ receptor agonist baclofen inhibits transient LES relaxation but it is not an ideal agent due to central nervous system activity. Lesogaberan (AZD3355) is a peripherally restricted $GABA_B$ receptor agonist with limited central nervous system activity that inhibits transient LES relaxation in dogs. In the present study, the comparative effects of lesogaberan (7 μmol/kg) and baclofen (2.8 μmol/kg) on reflux were studied in dogs using 24-h pHmetry. Drugs (or vehicle control) were administered orally prior to the first meal of the day, and the number of reflux episodes (pH<4 for ≥5 s) and acid exposure time were computed for the 24-h monitoring period. The mean (S.E.M.) number of reflux episodes/24 h was 4.6 (0.4) and 6.4 (0.6) for lesogaberan and baclofen, respectively, versus 10.7 (0.5) for control ($P<0.0001$ for both). Acid exposure time was 51.2 (4.5) min for control versus 23.6 (3.8) min for lesogaberan ($P<0.0001$) and 35.4 (6.5) min with baclofen ($P=0.05$). It is concluded that lesogaberan significantly reduces acid reflux in dogs, with comparable efficacy to baclofen.

1. Introduction

The advent of proton pump inhibitors set a landmark in the pharmacotherapy of gastroesophageal reflux disease, and the majority of patients with reflux disease achieve a good symptomatic response while on proton pump inhibitor therapy. However, 20–30% of patients continue to experience troublesome reflux symptoms despite taking a proton pump inhibitor daily (Fass, 2007). It is evident that multiple causalities are involved in reflux that may be refractory to proton pump inhibitor therapy, including reflux of weakly or non-acidic gastric juice (Koek et al., 2003; Vela et al., 2003) and proximal migration of refluxate (Zerbib et al., 2008). Consequently, a clear medical need exists for new therapies aimed at reducing reflux irrespective of the chemical composition of the refluxate.

The $GABA_B$ receptor is expressed in vagal afferents (Smid et al., 2001), and there is functional evidence that $GABA_B$ receptor agonists can stimulate the receptor on mechanosensitive gastric vagal afferents (Page and Blackshaw, 1999; Partosoedarso et al., 2001; Smid et al., 2001). Indeed, $GABA_B$ receptor agonism is now widely recognised as the most promising physiological approach to treating gastroesophageal reflux disease by reducing the incidence of transient lower esophageal sphincter (LES) relaxation (Lehmann, 2009), a major underlying cause of reflux disease (Dent, 2008).

The $GABA_B$ receptor agonist baclofen is a skeletal muscle antispastic agent that is also effective in reducing the number of transient LES relaxations in patients with gastroesophageal reflux disease (van Herwaarden et al., 2002; Zhang et al., 2002). It reduces acid and weakly/non-acidic reflux (Vela et al., 2003) as well as bile reflux (Koek et al., 2003), and more importantly, baclofen affords relief from symptoms of reflux disease (Ciccaglione and Marzio, 2003; Koek et al., 2003; Vela et al., 2003). The concept of treating patients with an insufficient response to proton pump inhibitors with an agent reducing transient LES relaxations has found experimental support in that baclofen reduces remaining symptoms of reflux disease in patients not achieving full symptomatic relief from omeprazole therapy (Koek et al., 2003). Interestingly, the pharmacodynamic effect of baclofen is unaffected by the presence of hiatal hernia (Beaumont and Boeckxstaens, 2009), negating previous speculation that an inhibitor of transient LES relaxations would not be very effective in such patients (Murray and Camilleri, 2000).

One major drawback associated with baclofen as a therapeutic agent for gastroesophageal reflux disease is its propensity to cause central nervous system (CNS) side-effects. Peripherally restricted

☆ This study has previously been presented in abstract form at Digestive Disease Week (2001 and 2008).

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Table 1
Effect of lesogaberan and baclofen on gastroesophageal acid reflux during 24-h pHmetry.

Dog	Treatment vehicle				Lesogaberan				Baclofen			
	# of reflux episodes	Acid exposure time (min) pH<4	Latency (min)	Clearance	# of reflux episodes	Acid exposure time (min) pH<4	Latency (min)	Clearance	# of reflux episodes	Acid exposure time (min) pH<4	Latency (min)	Clearance
#1 mean (S.E.M.)	12.9 (0.8)	63.1 (9.6)	129.0 (30.3)	5.0 (0.7)	7.6 (0.5)	21.4 (3.2)	263.0 (37.1)	3.9 (0.5)	8.2 (1.9)	47.3 (13.4)	292.2 (40.0)	6.6 (1.6)
Range	7–18	12.0–146.0	15.0–478.0	1.3–11. 1	5–10	7.0–37.0	125.9–408.0	1.4–6.2	4–17	21.0–103.0	182.0–397.0	1.8–12.9
#2 mean (S.E.M.)	6.8 (1.6)	66.6 (22.7)	190.9 (90.5)	8.7 (2.6)	3.3 (0.9)	62.3 (23.8)	262.7 (168.5)	25.6 (14.3)				
Range	1–16	0–188.0	68.0–821.0	0–21.0	2–5	24.0–106.0	0.2–577.0	4.8–53.0				
#3 mean (S.E.M.)	12.8 (1.2)	44.3 (12.3)	79.3 (13.2)	3.3 (0.8)	7.7 (0.3)	39.7 (18.4)	233.7 (29.0)	5.3 (2.5)				
Range	8–18	9.0–97.0	1.0–121.0	0.9–6.9	7–8	3.0–60.0	180.0–280.0	0.4–8.6				
#4 mean (S.E.M.)	9.7 (0.7)	74.9 (13.6)	112.5 (14.8)	8.3 (1.5)	3.2 (0.6)	23.2 (11.3)	435.8 (83.9)	6.1 (2.2)	6.0 (0.7)	30.4 (10.5)	420.1 (47.2)	6.1 (2.3)
Range	3–14	25.0–231.0	32.0–308.1	2.9–25.7	1–6	0–111.0	5.2–1059.0	0.3–22.2	4–9	4.0–74.0	248.0–623.0	0.6–14.8
#5 mean (S.E.M.)	9.8 (1.1)	26.1 (5.7)	119.8 (18.6)	2.9 (0.6)	3.3 (0.7)	7.0 (3.5)	350.2 (146.6)	2.1 (0.8)				
Range	5–14	7.0–67.0	22.0–219.0	0.6–5.2	2–4	3.0–14.0	107.4–613.9	0.8–3.5				
#6 mean (S.E.M.)	3.1 (0.6)	35.1 (17.1)	533.8 (188.8)	11.3 (5.0)	1.0 (0.0)	2.5 (2.5)	553.3 (179.4)	2.5 (2.5)				
Range	0–5	0–123.0	31.0–1440.0	0.6–30.8	1–1	0–5.0	373.9–732.7	0–5.0				
#7 mean (S.E.M.)	18.1 (1.5)	95.4 (19.8)	90.0 (26.6)	5.2 (1.0)	6.5 (1.4)	39.2 (25.3)	236.2 (116.6)	5.3 (3.2)	7.7 (2.4)	56.1 (22.7)	263.0 (90.4)	6.2 (2.0)
Range	12–23	55.0–181.0	22.0–194.0	2.6–8.8	1–10	0–164.0	25.0–310.0	0–20.5	1–18	2.0–133.0	58.0–714.0	0.7–16.6
#8 mean (S.E.M.)	17.0 (2.1)	49.7 (16.6)	58.7 (16.3)	2.7 (0.8)	5.8 (0.5)	26.6 (5.1)	151.5 (49.6)	4.7 (0.9)	7.2 (1.2)	44.2 (22.2)	318.3 (29.1)	6.0 (3.1)
Range	8–20	10.0–125.0	13.0–116.0	0.7–6.3	4–8	5.0–44.0	9.0–371.0	1.0–9.0	3–11	0–147.0	246.0–430.0	0.1–21.0
#9 mean (S.E.M.)	9.9 (1.2)	21.2 (5.1)	178.3 (27.0)	2.0 (0.3)	3.8 (1.0)	20.1 (8.0)	548.9 (125.1)	5.0 (1.6)	4.9 (0.7)	15.7 (9.4)	516.6 (89.6)	2.5 (1.3)
Range	4–19	3.0–65.0	55.0–434.0	0.8–4.0	0–8	0–73.0	147.0–1440.0	0.0–13.0	2–7	1.0–69.0	188.0–919.0	0.3–9.9
#10 mean (S.E.M.)	8.9 (1.0)	33.7 (8.9)	132.2 (61.4)	3.8 (0.9)	1.7 (0.4)	4.3 (3.8)	457.9 (184.8)	1.8 (1.5)	4.4 (0.7)	16.0 (4.8)	510.6 (143.6)	3.5 (1.0)
Range	4–14	5.0–104.0	0–643.0	1.0–9.5	0–3	0–27.0	13.0–1440.0	0.0–9.0	4–6	3.0–29.0	320.0–1077.0	1.5–5.8
Total mean (S.E.M.)	10.7 (0.5)	51.2 (4.5)	153.8 (19.6)	5.2 (0.5)	4.7 (0.4)[b]	23.6 (3.9)[b]	351.0 (38.3)[b]	5.5 (1.0)	6.4 (0.6)[b]	35.4 (6.5)[a]	384.6 (34.3)[b]	5.2 (0.8)
Range	0–23	0–231.0	1.0–1440.0	0–30.8	0–10	0–164.0	0.2–1440.0	0–53.0	1–18	0–147.0	58.0–1077.0	0.1–21.0

[a] $P \leq 0.05$ versus control.
[b] $P < 0.0001$ versus control.

$GABA_B$ receptor agonists that do not activate central $GABA_B$ receptors may, therefore, offer the desired effects in the absence of central side-effects. Lesogaberan (AZD3355), a novel $GABA_B$ receptor agonist that reduces the incidence of transient LES relaxations in dogs with a low potency for CNS adverse effects (Lehmann et al., 2009), may be one such agent. Lesogaberan penetrates the blood-brain barrier poorly, and the small fraction that does access the brain is prevented from activating the central $GABA_B$ receptors because of cellular uptake (Lehmann et al., 2009).

Short-term stationary measurements are not optimally designed for evaluation of net effects of compounds such as lesogaberan or baclofen on esophageal acid exposure. In order to address this issue, we have for the first time measured the effects of lesogaberan and baclofen on 24-h esophageal acid reflux in freely moving dogs. Because of a possibility that baclofen may have an effect on gastric acid secretion (Ciccaglione and Marzio, 2003), intragastric pH was measured in a subset of experiments after a higher dose of baclofen.

2. Materials and methods

Ten adult Labrador retriever dogs (Terje Gammelsrud, Löken Gård ANS, 1878 Herland, Norway and Rååhöjdens kennel, Rååhöjden, Sweden) of either gender (5 males and 5 females) were used. The dogs weighed 22–35 kg and were 2–7 years old. Cervical esophagostomy was performed, and dogs were allowed to recover for at least 2 weeks after surgery.

After recovery, dogs were intubated with an antimony pH electrode with the tip positioned 4 cm above the upper margin of the LES, the location of which had been determined previously using manometry. In some experiments, the electrode was placed 8 cm below the sphincter to record intragastric pH. The electrode was calibrated at pH 1 and 7 before the experiment and checked for drift after the 24-h recording session. For collection of pH data during the 24-h monitoring period, the electrode was connected to a Digitrapper MKIII (Medtronic Synectics AB, Stockholm, Sweden) that was placed in a pocket of a specially designed vest.

After an overnight fast, vehicle (0.9% NaCl, 2 ml/kg), lesogaberan (7 μmol/kg; AstraZeneca R&D, Mölndal, Sweden) or racemic baclofen (2.8 μmol/kg; RBI, Natick, MA, USA) was administered orally in the morning. The doses were chosen so that they would approximate ED_{50} with respect to inhibition of transient LES relaxation (Lehmann et al., 2009). A higher dose of baclofen (7 μmol/kg, orally) was given in the experiments in which intragastric pH was measured. In pilot experiments, it was found that the standard diet of dry pellets elicited very little acid reflux but that ground beef was more effective, so a meal consisting of 250 g ground beef was served 30 min after oral dosing, and this was repeated three times with a 4-h interval so that the last meal was served at approximately 9.00 PM. Water was freely available during the entire experiment. A total number of 201 experiments were performed (vehicle, $n=102$; lesogaberan, $n=61$; and baclofen, $n=38$). All dogs had previously been used in experiments involving experimental drugs, but the minimum wash-out period was 4 days.

The 24-h recordings were analysed with Polygram 98 (Medtronic Synectics AB, Stockholm, Sweden) and Pharmlab (specially designed by AstraZeneca R&D, Mölndal, Sweden) software. Acid reflux was defined as esophageal pH<4 lasting for at least 5 s, with an interval of at least 5 s between episodes. Acid exposure was calculated as the time with pH<4 in relation to the esophagus, or pH<2, 3 or 4 in relation to the stomach. Acid clearance (acid exposure time/reflux episode) was calculated as the total duration of acid exposure/number of reflux episodes for each experiment. Latency to first reflux episode was calculated as the time between the first meal and the first episode.

Data are expressed as mean ± S.E.M., and the unpaired Student's *t*-test was used for statistical comparisons.

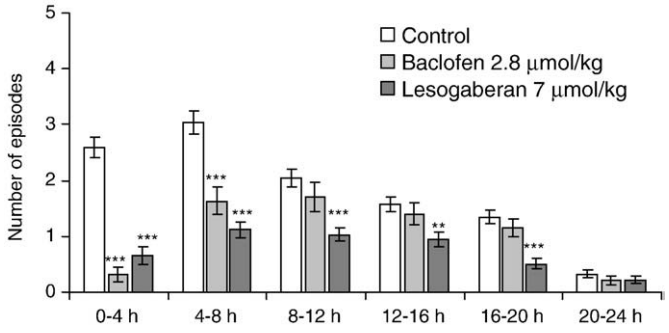

Fig. 1. Mean (±S.E.M.) number of acid reflux episodes (pH<4) during 24-h pHmetry in freely moving dogs; $^{**}P<0.01$, $^{***}P<0.001$ versus control.

All experiments were approved by the ethical committee for animal experiments in the Göteborg region.

3. Results

The effects of lesogaberan and baclofen on acid reflux are summarised in Table 1. Both group data as well as individual results are shown. Overall, the mean number of reflux episodes during the 24-h monitoring period was significantly lower with lesogaberan (4.6 ± 0.4) and baclofen (6.4 ± 0.4) versus vehicle control (10.7 ± 0.5; both $P<0.0001$). Total acid exposure was also reduced with the $GABA_B$ receptor agonists relative to control: mean time with pH<4 was 51.2 ± 4.5 min for control, compared with 23.6 ± 3.9 min for lesogaberan ($P<0.0001$) and 34.4 ± 6.5 min for baclofen ($P<0.05$). Latency to first post-prandial reflux episode was significantly prolonged after administration of lesogaberan and baclofen (both $P<0.0001$ versus control). Acid clearance time was not significantly different between the control and treatment groups, ranging from 5.2 ± 0.5 min for control to 5.5 ± 1.0 min for lesogaberan. The statistically significant inhibitory effect of lesogaberan on reflux episodes was maintained for up to 20 h after administration, whereas the inhibitory effect of baclofen was only statistically significant for the first 8 h (Fig. 1).

Baclofen did not affect intragastric pH, which was below 4 for 67 ± 8% of the time in the control group and 59 ± 13% of the time in the baclofen group. These data were acquired from a cohort of 4 dogs, and the experiment was repeated in each dog at 4 and 2 separate occasions in the placebo and baclofen groups, respectively. Similarly, analysis using other limits (pH<3 and <2) did not reveal any differences between the groups.

No side-effects were noted in any of the experimental series confirming previous work (Lehmann et al., 2009).

4. Discussion

There is a paucity of data on 24 h acid reflux in freely moving dogs. McMahon et al. (2002) reported 24 h esophageal reflux indices in female mongrel dogs and, in line with our observations, found that the numbers of acid reflux episodes were very low (6.7/24 h) when the dogs were offered dry pellets. We optimised our model by feeding the dogs with ground beef that induced more reflux so that inhibitory effects of lesogaberan and baclofen could be recorded with greater precision. Kazachkov et al. (2008) recently observed a very low acid exposure in freely moving dogs, 0.46% compared to 3.6% in the current study. There was no information whether the dogs were fed ad libitum or if they were denied access to food so it is difficult to compare their results with those from our study.

The current investigation has shown that lesogaberan and baclofen both significantly inhibit gastroesophageal acid reflux in freely moving dogs over a 24-h period. While the compounds produced comparable reduction of reflux and esophageal acid exposure, lesogaberan had the longest duration of action, and

maintained a significant inhibitory effect on the number of reflux episodes for 12 h longer than baclofen. Other findings included prolonged latency to the first reflux episode and unaltered acid clearance with both compounds, and no effect of baclofen on intragastric pH.

So far, the quantitative relationship between inhibition of transient LES relaxations and acid exposure has been a matter of speculation. The data from the present study suggest that a dose of a reflux inhibitor that affords some 50% inhibition of transient LES relaxations (Lehmann et al., 2009) translates into a similar degree of reduction of esophageal acid exposure. This information is valuable for the design of clinical trials on reflux inhibitors in terms of dose-setting, but differences in pharmacokinetics between dogs and humans have to be considered. However, given the fact that the plasma half-life for lesogaberan is shorter in dogs (Lehmann et al., 2009) than in humans (AstraZeneca, data on file), lower doses may be expected to be equally effective in humans.

While the mechanism of action of lesogaberan and baclofen was not addressed in this study, an inhibitory effect on transient LES relaxation is the most likely explanation. Baclofen increases basal LES pressure in healthy individuals and patients with gastroesophageal reflux disease alike (Lee et al., 2003; Zhang et al., 2002), but not in dogs in stationary measurements (Lehmann et al., 1999). The basis for the species difference is not known, but it may relate to the fact that the basal LES pressure is much higher in dogs [approximately 40 mmHg (Lehmann et al., 1999)] than in humans [10 mmHg in healthy subjects (Lidums et al., 2000)]. The possibility that some of the effects of baclofen and lesogaberan on reflux actually relates to effects on basal LES pressure cannot be excluded. If this is the case, it is probably a minor contributor unless non-transient LES relaxation-related reflux mechanisms are more important in the ambulatory compared to the stationary setting in dogs.

Baclofen has been shown to powerfully enhance gastric acid secretion in fasting humans (Pugh et al., 1985). However, if this were the case post-prandially, transient LES relaxations may be expected to be more frequently associated with acid reflux after baclofen, which is not the case (Lidums et al., 2000; Zhang et al., 2002). In our study, baclofen did not change intragastric pH, indicating that acid secretion was not affected. This is in contrast to previous findings demonstrating a stimulatory effect of baclofen in dogs with a gastric fistula or Heidenhain pouch (Thirlby et al., 1988). In humans, however, baclofen raised intragastric pH only slightly (Ciccaglione and Marzio, 2003). Whatever the case, it appears that any action of baclofen on gastric acid secretion does not have any meaningful impact on gastroesophageal reflux. The effects of lesogaberan on intragastric pH were not studied since the racemate of lesogaberan (Lehmann et al., 2009) does not affect gastric acid secretion in conscious rats (Lehmann, unpublished own observations).

The observation that lesogaberan significantly reduces esophageal reflux and duration of esophageal acid exposure over 24 h in ambulatory dogs offers additional incentives for clinical development of this compound. Interestingly, the duration of action of lesogaberan on acid reflux greatly exceeded the drug's plasma half-life, which in the dog is about 7 h. While it cannot be excluded that the prolonged effect is related to active metabolite(s), it is highly unlikely because of the narrow structure-activity of the $GABA_B$ receptor (Alstermark et al., 2008). Interestingly, the 4-h half-life of baclofen in the dog is shorter than the duration of inhibition of transient LES relaxations (Lehmann et al., 1999).

While this study was confined to measurement of acid reflux, it is very likely that inhibition of reflux of weakly acidic or non-acidic gastric juice would be of a similar magnitude. Indeed, a stationary pH-metric/impedance study provided evidence that baclofen reduces reflux to a similar extent irrespective of the pH of the refluxate (Vela et al., 2003).

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