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Evaluation of the effect of oral omeprazole on canine cerebrospinal fluid production: A pilot study

M. Girod [a,*], F. Allerton [a], K. Gommeren [a], A.C. Tutunaru [a], J. de Marchin [b], I. Van Soens [a], E. Ramery [a], D. Peeters [a]

[a] Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Liège, Boulevard de Colonster 20, 4000 Liège, Belgium
[b] Labocit, Citadelle Hospital, Boulevard du 12ème de Ligne 1, 4000 Liège, Belgium

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ABSTRACT

Administration of omeprazole by ventriculo-cisternal perfusion or intravenously has been shown to decrease cerebrospinal fluid (CSF) production in dogs and rabbits. Oral omeprazole has consequently been recommended to reduce CSF production in dogs with conditions in which clinical signs may be attributable to an accumulation of CSF in the central nervous system (e.g. hydrocephalus, syringomyelia). The albumin quotient (QAlb), the ratio between CSF and serum albumin concentration, has been proposed as a reliable means to evaluate CSF production; decreasing CSF production should cause an increase in QAlb.

The aims of this study were to assess the effect of oral administration of omeprazole on QAlb in dogs and to compare two methods to assess CSF albumin concentration. Fifteen healthy Beagle dogs received omeprazole (1.2 mg/kg/day) orally for 14 days; CSF and blood were obtained before and after treatment. CSF albumin concentrations were evaluated by nephelometry and high-resolution protein electrophoresis. Regardless of the method used for measuring albumin, QAlb did not change significantly following oral omeprazole administration, suggesting that CSF production in healthy dogs may not be affected by chronic oral therapy with omeprazole.

Introduction

Omeprazole is a substituted benzimidazole that inhibits the H^+-K^+ ATPase pumps of gastric parietal cells and is used as an effective anti-ulcer therapy in people and companion animals worldwide (Hersey and Sachs, 1995). Two experimental studies have demonstrated that omeprazole can significantly decrease cerebrospinal fluid (CSF) production (by 26–50%) following ventriculocisternal (VC) or intravenous (IV) administration in dogs and rabbits (Lindvall-Axelsson et al., 1992; Javaheri et al., 1997). However, the mechanism by which omeprazole affects CSF production was not elucidated in these studies. Moreover, despite the fact that both studies only focused on the immediate effect of IV or VC administration of omeprazole on CSF production, oral administration (0.5–1.5 mg/kg/day) is currently recommended for the long-term management of dogs with hydrocephalus or syringomyelia (Rusbridge et al., 2006; Thomas, 2010; Plessas et al., 2012).

Hydrocephalus and syringomyelia are two conditions in which a disturbance in CSF flow may provoke clinical signs in affected dogs. Hydrocephalus is a multi-factorial disease involving distension of the ventricular system with an increased volume of CSF. Obstructive hydrocephalus, the most common form, occurs secondary to the inadequate passage of CSF from its site of production to its absorption site (DeLahunta and Glass, 2009; Rekate, 2009; Thomas, 2010). A developmental form of obstructive hydrocephalus is observed in toy and brachycephalic breeds although the pathophysiology is not completely understood. The most common causes identified are stenosis of the mesencephalic aqueduct or malformations of the arachnoid villi (DeLahunta and Glass, 2009; Thomas, 2010). Neoplasia or inflammatory disease may also interfere with CSF flow causing acquired hydrocephalus.

Syringomyelia is a complex disease in which a reduced cross-sectional area of the subarachnoid space contributes to altered CSF dynamics leading to the formation of fluid-cavitation in the spinal cord. In dogs, syringomyelia may result from congenital cervical malformations or subarachnoid diverticula. It may also occur secondary to acquired disorders such as intervertebral disc disease or intracranial neoplasia. The fluid accumulation in the spinal cord has been associated with pain or dysaesthesia (Rusbridge et al., 2007; Hu et al., 2012; Driver et al., 2013). In both conditions, the principal goals of medical management are to decrease CSF production, reduce CSF accumulation in the ventricular system or spinal cord, and decrease CSF turbulence (Rusbridge and Jeffery, 2008; Thomas, 2010; Driver et al., 2013).

* Corresponding author. Tel.: +324 93 50 48 14.
E-mail address: maudgirod@msn.com (M. Girod).

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The VC perfusion technique is a well-established method to assess CSF production rate. However, because the technique is invasive, it is only applicable in experimental studies (Pappenheimer et al., 1961; Lindvall-Axelsson et al., 1992; Javaheri et al., 1997) and an alternative method is required for clinical research on this topic. The albumin quotient (QAlb) is the ratio between CSF and serum albumin concentrations (Olsson and Pettersson, 1976; Reiber, 1994) and is considered to be a reliable indicator of CSF flow rate in human medicine (Reiber et al., 1993; Reiber, 1994, 2003). Any decrease in CSF production should theoretically be accompanied by an increase in QAlb (Reiber, 2003).

The aim of the present study was to determine QAlb values before and after oral administration of omeprazole in healthy dogs. We hypothesised that QAlb (a surrogate marker of CSF production) would increase following omeprazole administration if oral omeprazole effectively decreases CSF production. Several parameters other than QAlb were measured on blood and CSF samples to investigate potential mechanisms by which omeprazole would change CSF flow. A second goal was to look at the correlation between high-resolution protein electrophoresis and nephelometry in assaying CSF albumin.

Materials and methods

Animals

The study was conducted with approval from the Ethical Committee for Experimental Animals of the University of Liège (Record Number: 1370). All experiments were performed under general anaesthesia and animal welfare was safeguarded throughout the study. Fifteen experimental Beagle dogs, eight entire females and seven entire males aged 6–13 years (mean 7.9 ± 2.4 years old) and weighing 14.2–22.1 kg (mean 17.3 ± 2.6 kg) were used. All dogs were clinically healthy at physical examination.

Experimental design

Blood and CSF sampling were performed in all dogs before and after 14 days of oral omeprazole administration. In each dog, omeprazole (Omeprazole Mylan 10 mg) was administered orally at a dose of 1–1.40 mg/kg once daily (mean 1.20 ± 0.16 mg/kg once daily). Dogs were clinically examined every day throughout the study period.

CSF albumin concentrations were evaluated by nephelometry and high-resolution protein electrophoresis on paired CSF and serum samples, according to guidelines from the International Consensus Group for CSF Analysis (Reiber et al., 2003). CSF was checked for blood contamination or subclinical signs of inflammation by performing erythrocyte and leukocyte counts. Serum and CSF electrolyte, total protein, glucose and lactate concentrations, as well as pH and plasma osmolality were also determined.

Samples

Blood and CSF sampling were performed under general anaesthesia, maintained with isoflurane (Isovet, Piramal Healthcare UK: 1.5%; oxygen at 0.8 L/min), after IV premedication with methadone (Comfortan Eurovet; 0.4 mg/kg) and induction with IV propofol (Diprivan AstraZeneca; 5 mg/kg bolus). During the procedure, oxygen saturation was maintained over 96% and end tidal CO_2 between 35 and 45 mm Hg. Rectal temperature was measured to allow for correction of the measured pH.

From each dog, 2.2–2.5 mL of CSF was collected from the cerebellomedullary cistern and placed into two 1.8 mL microcentrifuge tubes (Cryotubes). Blood was sampled via jugular venepuncture immediately after obtaining the CSF sample. One sample of blood and CSF was immediately assayed for erythrocyte and leukocyte count and pH, lactate, glucose, total protein and electrolyte measurements. The second CSF tube was cooled (at 4 °C) for 24 h prior to nephelometric albumin measurement. An aliquot of the remainder of the CSF and a serum sample were frozen (–20 °C for 1 month) for high-resolution protein electrophoresis.

Analyses

CSF and venous blood pH were measured using a pH meter (Mettler Toledo MP225) directly after collection. Each value was corrected with the Rosenthal factor to allow for the difference between the temperature of the patient and that of the measuring device:

$$\text{Blood pHt1} = \text{Blood pHt2} - 0.0147(t1 - t2)$$

where t1 represents the rectal temperature of the dog, t2 the temperature of the meter's electrode (37 °C), blood pHt2 the pH reading by the electrode at 37 °C and blood pHt1 the pH of the dog's blood.

Osmolality was measured by freezing point depression (Osmo station OM-6050 Menarini). Serum albumin and total protein concentrations were measured using a colorimetric reaction with bromocresol green technique (Response 920, Diasys). Red and white blood cells in CSF were counted using an automated analyser (Cell-Dynn 3700). CSF total protein concentrations were measured by a colorimetric reaction with pyrogallol red (Cobas Mira, Roche) (Behr et al., 2003).

High-resolution agarose gel electrophoresis was performed on paired CSF and serum samples, after thawing, using a commercially available agarose gel (Hydragel protein K20, Dyasis on Cobas mirror). A concentration step was performed on CSF samples using a membrane microconcentrator technique (Vivaspin 500 VS0101, Sartorius). Paired CSF and serum samples were analysed during the same analytical run and results were read by a semiautomatic system. The albumin concentrations in serum and CSF were calculated by multiplying the total protein concentration of the sample by the percentage value of the albumin from high-resolution protein electrophoresis.

CSF albumin concentration was also determined by nephelometry, as previously described (Fink et al., 1989). A calibration of the human nephelometric assay (BNII system, Kit N AS ALB, Siemens Healthcare) was deemed necessary because the monoclonal antibody against human albumin used in the assay shared only a partial cross-reactivity with canine albumin (Gentilini et al., 2005; Murgier et al., 2009). A calibration curve was constructed by diluting a solution of purified canine albumin (Canine Albumin Protein ab119814, Abcam) to concentrations varying between 1.6 and 100 mg/dL using 0.9% saline. Linearity was determined by comparing measured albumin concentrations with those expected. Each measurement was performed in duplicate. A standard curve with four points of calibration was obtained and demonstrated excellent linearity in the range of 12.5–100 mg/dL (Fig. 1). Dilutions beyond 12.5 mg/dL were below the threshold of detection of the assay.

QAlb was calculated as the ratio between CSF and serum albumin concentrations:

$$\text{QAlb} = (\text{CSF Albumin}\,[\text{g/L}])/(\text{Serum Albumin}\,[\text{g/L}])$$

Two values of QAlb were determined: the first (QAlb1) was calculated from concentrations of CSF and serum albumin as determined by high-resolution protein electrophoresis, and the second (QAlb2) using the concentration of CSF albumin determined by the nephelometric assay and the concentration of serum albumin determined with the bromocresol green technique.

Statistical analyses

A statistical analysis program (Sigmastat 3.5 Software) was used for calculations. Continuous data were analysed for normality using a Kolmogorov–Smirnov test. All data were expressed as means ± SD. A paired *t* test was used to compare results before and after treatment for parametric data. If data assumed a non-normal distribution, the Wilcoxon Signed Rank test was used. A Pearson product moment correlation was performed to compare the results obtained with the two techniques (high-resolution protein electrophoresis and nephelometry assay) used for the determination of albumin concentration.

To investigate the effect of age on QAlb, the dogs were separated into three groups according to age. The first group was composed of eight dogs of 6 years of age; the second group was composed of three dogs that were 8.5 years old and the last group included four older dogs (two 10.5-year-old dogs, one 11-year-old dog and one 13-year-old dog).

A Kruskal–Wallis test was used to compare QAlb according to age. Results were considered to be statistically significant at a P value <0.05.

Results

CSF albumin concentration and QAlb

All electrophoresis profiles were considered interpretable with a clear cut-off allowing determination of albumin concentration. Each dog presented a type 1 protein electrophoresis profile consistent with those previously described in healthy dogs (Behr et al., 2006) (Fig. 2).

There was a strong correlation between HRE and nephelometry in determining CSF albumin concentration (correlation coefficient = 0.86, $P < 0.0001$) (Fig. 3). Compared with the nephelometric assay, high-resolution protein electrophoresis consistently underestimated CSF albumin concentrations.

There was no significant difference in QAlb before and after omeprazole administration regardless of the method used to calculate QAlb (Table 2). When dogs were classified into three groups according to their age, we observed an increase in QAlb with

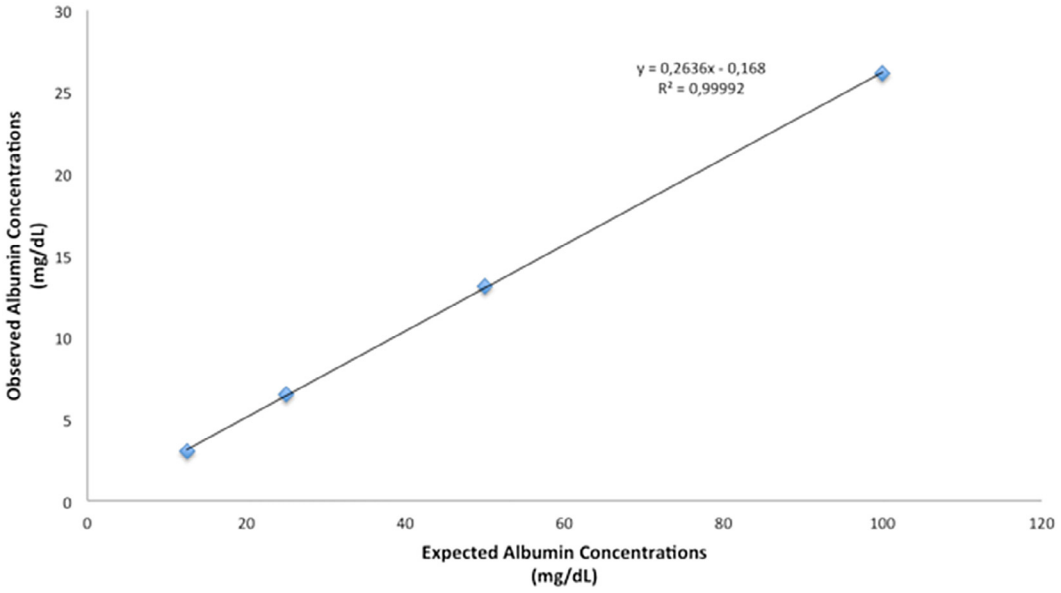

Fig. 1. Canine calibration curve obtained for the automated nephelometric assay. The calibration curve was constructed by diluting a solution of purified canine albumin (expected albumin concentrations).

increasing age but the difference between groups was not statistically significant (Fig. 4).

Changes in CSF and blood composition

No macroscopic blood contamination was observed in any CSF sample. The number of erythrocytes in the CSF varied between 0 and 7000/μL with no significant difference between median red blood cell counts before and after omeprazole administration. CSF pH, white blood cell count, lactate, glucose and total protein concentrations were within normal limits in each dog and did not show significant changes after omeprazole administration. A minimal yet statistically significant increase in CSF Na^+ concentration was observed after omeprazole administration (CSF-Na^+ pre-omeprazole = 144.3 ± 1.9 mmol/L; CSF-Na^+ post-omeprazole = 145.9 ± 1.1 mmol/L; $t = -2.976$; $P = 0.010$) (Table 1).

Blood venous pH was slightly but statistically significantly increased after omeprazole administration (pre-omeprazole = 7.43 ± 0.05; post-omeprazole = 7.50 ± 0.04; $t = -4.111$; $P = 0.001$). Serum electrolyte concentrations did not differ significantly between day 0 and day 14 except for a mild decrease in serum Cl^- concentration after omeprazole administration (pre-omeprazole = 105.3 ± 1.7 mmol/L; post-omeprazole = 103.3 ± 1.2 mmol/L; $Z = -2.866$; $P = 0.003$). No other variable was significantly different following omeprazole administration (Table 2).

Discussion

The present study is the first to report the effect of omeprazole on CSF production in dogs by using QAlb as a surrogate marker of CSF production and we found no change in QAlb after 14 days of oral omeprazole administration. It has been previously established in human medicine that any decrease in CSF production will cause an increase in QAlb in both physiological and pathological conditions (Reiber, 1994, 2003; Reiber and Peter, 2001).

Albumin in CSF originates from blood only and reaches CSF by numerous pathways at the level of the ventricles (i.e. at the level of the choroid plexus, the ventricular surface and the circumventricular organs), the cisterns or the lumbar and cortical subarachnoid space (Reiber, 2003). Blood-derived protein dynamics in CSF is defined by the molecular flux/CSF flow theory in which proteins diffuse passively from blood into CSF according to a controlled molecular size-dependent process (Felgenhauer, 1974; Reiber, 2003). Any increase in blood proteins is accompanied by an increase in CSF proteins. Thus, QAlb is independent of blood changes and is a relevant predictor of CSF flow rate (Reiber, 1994, 2003).

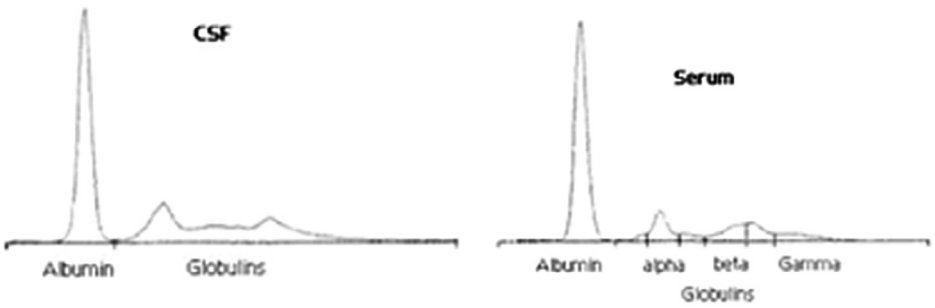

Fig. 2. CSF and serum protein electrophoretic profiles in one healthy dog. Similar profiles were observed in all dogs and were all of type 1 (no globulin peak observed in either CSF or serum). No profile was considered non-interpretable (type 4).

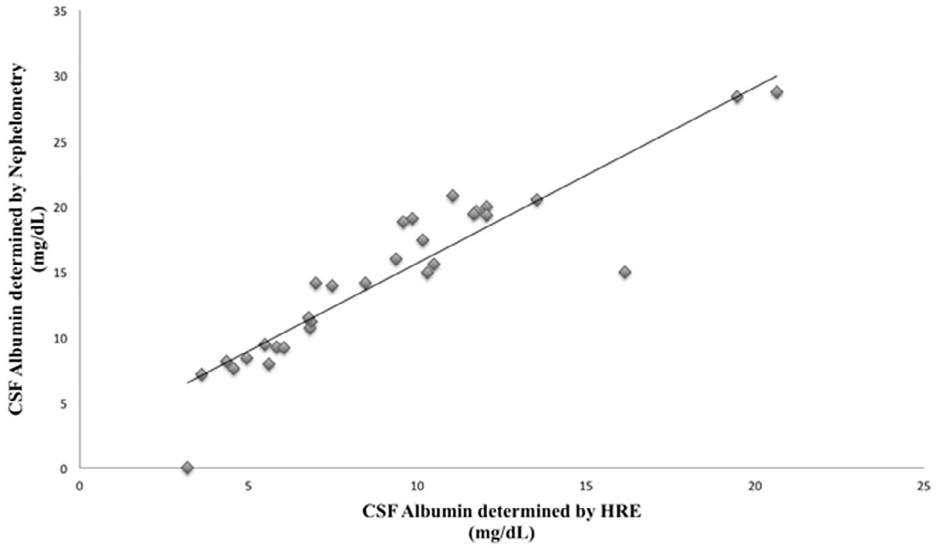

Fig. 3. Correlation between CSF albumin concentration measurements obtained by nephelometry and by high-resolution electrophoresis (HRE). There was a strong correlation between HRE and nephelometry to determine CSF albumin concentration (correlation coefficient = 0.86, $P < 0.0001$).

Without CSF flow, proteins would diffuse from blood into CSF until reaching equilibrium, as has been observed after death (Reiber, 2003). Therefore, a decrease in CSF production is accompanied by an increase in CSF protein concentrations (Reiber, 2003). The absence of any change in QAlb after 2 weeks oral administration of omeprazole could be interpreted as an absence of a sustained effect of omeprazole on CSF production. The absence of an effect of oral administration of omeprazole on QAlb could perhaps also be due to low study power (type II error), although power calculations based on previous data suggested we recruited a sufficient number of dogs.

The application of QAlb measurements in an experimental setting enabled us to evaluate the effect of omeprazole on CSF production without the need for invasive or CSF volumetric measurement. CSF volumetric techniques using CT or MRI have been reported in dogs (Daniel et al., 1995; Vite et al., 1997). However, to the best of our knowledge, a link between CSF production and ventricular volume has not been established in dogs. For this reason, imaging techniques were not pursued in this study.

The absence of an effect of omeprazole on CSF production contrasts with previous studies in which omeprazole decreased short-term CSF production in an experimental design. Lindvall-Axelsson et al. (1992) were the first to assess the effect of omeprazole on CSF production. They showed that omeprazole caused a dose-related reduction in CSF production in rabbits and they established an approximate minimum dose of 10^{-8} mol/L when it was used VC. They also demonstrated that an IV dose (0.2 mg/kg) of omeprazole decreased CSF production by 25% in rabbits. Javaheri et al. (1997) performed a similar study in dogs. They showed a significant reduction (~26%) in CSF production after adding 10^{-5} mol/L of omeprazole to anaesthetised dogs by VC perfusion. An insufficient CNS concentration of omeprazole following oral administration might have accounted for the lack of change in QAlb: the absence of measurement of CSF omeprazole concentrations is a limitation of our study.

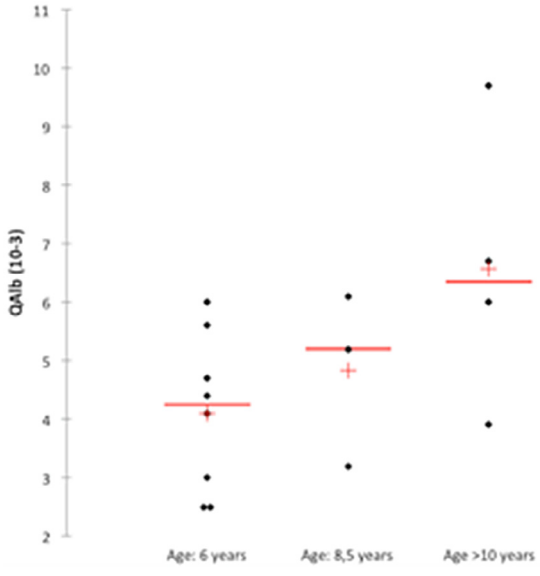

Fig. 4. Scatterplot showing the albumin quotient (QAlb) for different age-grouped healthy Beagle dogs. Dogs were separated into three groups according to age (eight dogs of 6 years of age; three dogs of 8–9 years old and four dogs older than 10 years). The cross (+) represents the mean value and the horizontal line represents the median. There was an increase but not statistically significant of QAlb with age in dogs ($P = 0.215$), suggesting a decrease in canine CSF production with age.

Table 1
Cerebrospinal fluid (CSF) values before (day 0) and after (day 14) oral administration of omeprazole (expressed as means ± standard deviation) in 15 healthy dogs. A paired *t* test was performed for parametric data whereas a Wilcoxon Signed Rank test was performed for non-parametric data (*). Only a slight increase in CSF sodium concentration and slight decrease in albumin concentration determined by nephelometry after omeprazole administration were found to be statistically significant (bold).

	Day 0	Day 14	*P*
pH	7.40 ± 0.03	7.41 ± 0.03	0.546
Cl^- (mmol/L)	131.1 ± 3.6	129.8 ± 5.1	0.445
Na^+ (mmol/L)	**144.3 ± 1.9**	**145.9 ± 1.1**	**0.01**
K^+ (mmol/L)	2.83 ± 0.08	2.87 ± 0.05	0.109*
Ca^{2+} (mmol/L)	1.27 ± 0.07	1.31 ± 0.08	0.123
WBC count (cells/μL)	2.47 ± 1.85	2.20 ± 1.57	0.662
Lactate (mmol/L)	1.90 ± 0.20	1.81 ± 0.13	0.252*
Glucose (mmol/L)	4.19 ± 0.29	4.16 ± 0.17	0.654
Total proteins (g/L)	0.184 ± 0.087	0.167 ± 0.079	0.151*
Albumin (g/L) determined by HRE	0.094 ± 0.043	0.089 ± 0.045	0.368
Albumin (g/L) determined by nephelometry	**0.154 ± 0.059**	**0.147 ± 0.060**	**0.005**

Table 2
Blood values before (day 0) and after (day 14) oral administration of omeprazole (expressed as means ± standard deviation) in 15 dogs. A paired *t* test was performed for parametric data whereas a Wilcoxon Signed Rank test was performed for non-parametric data (*). A significant mild increase in blood pH, a slight decrease in serum Cl^- concentrations and a slight decrease in albumin concentrations were observed after omeprazole administration (bold). QAlb1 was calculated from concentrations of CSF and serum albumin as determined by HRE, and QAlb2 was calculated using the concentration of CSF albumin determined by the nephelometric assay and the concentration of serum albumin determined with the bromocresol green technique. QAlb did not change significantly after oral administration of omeprazole for 14 days.

	Day 0	Day 14	*P*
Blood venous pH	**7.44 ± 0.05**	**7.50 ± 0.04**	**0.001**
Cl^- (mmol/L)	**105.3 ± 1.7**	**103.3 ± 1.2**	**0.003***
Na^+ (mmol/**L**)	144.9 ± 2.1	145.7 ± 2.0	0.217
K^+ (mmol/**L**)	3.82 ± 0.39	3.85 ± 0.20	0.658
Ca^{2+} (mmol/**L**)	2.52 ± 0.09	2.54 ± 0.12	0.600
Osmolality (mOsm/kg)	300.00 ± 3.40	300.73 ± 2.15	0.413
Haematocrit (%)	41 ± 5	42 ± 4	0.361
RBC count (10^{12} cells/**μL**)	5.79 ± 0.67	5.89 ± 0.54	0.122
WBC count (10^9 cells/**μL**)	7.34 ± 1.45	7.23 ± 1.07	0.791
Lactate (mmol/**L**)	1.23 ± 0.35	1.35 ± 0.35	0.181
Glucose (mmol/**L**)	5.64 ± 0.48	5.70 ± 0.40	0.518
Total proteins (g/**L**)	60.33 ± 3.81	59.73 ± 4.08	0.346
Albumin (g/L)	**31.33 ± 2.43**	**29.41 ± 2.37**	**<0.001**
QAlb1 ($\times 10^{-3}$)	2.69 ± 1.34	2.73 ± 1.45	0.966*
QAlb2 ($\times 10^{-3}$)	4.91 ± 1.90	4.99 ± 2.20	0.525

In the present study only the effect of prolonged exposure to omeprazole (14 days) was evaluated. Previous experiments have not investigated the effects of omeprazole beyond several hours. Development of drug tolerance is a potential explanation for the lack of change in QAlb after 2 weeks administration. Other drugs have shown opposing effects when given acutely versus chronically. Acute administration of ethanol reduced CSF production by about 40% whereas alcoholic humans present enlarged cerebral ventricles (potentially consistent with an increase in CSF production due to chronic ethanol exposure) (Javaheri and Corbett, 1998). A similar effect on CSF production has been observed with caffeine (Han et al., 2009; Wostyn et al., 2011). This 'effect inversion' of caffeine may be secondary to the modulation of the expression of Na^+-K^+-ATPase in the choroid plexuses by adenosine receptors (Han et al., 2009).

Puscas et al. (1999) demonstrated that omeprazole has the ability to inhibit carbonic anhydrases I, II and IV. Based on this hypothesis, Balakrishnan et al. (2001) studied the effect of omeprazole as an anticonvulsive agent in rats and demonstrated that omeprazole was a potentially effective antiepileptic drug that may act through the inhibition of brain carbonic anhydrase. However, rats developed a rapid tolerance and were refractory to repeated administration of omeprazole. It is possible that omeprazole decreases CSF production in acute conditions via inhibition of carbonic anhydrase but that tolerance may develop with chronic administration.

Several factors can interfere with CSF production and therefore might have masked the effects of omeprazole in our study. To avoid this, our experiment was carefully controlled: drugs used for anaesthesia were chosen because they were known not to interfere with CSF production (Artru, 1983, 1984, 1993) and experimental conditions were identical on day 0 and day 14.

Increased QAlb has been found in elderly people and is thought to be due to reduced CSF production (Reiber, 1994, 2003; Silverberg et al., 2003). The findings of an increase in QAlb with age in this study suggest the presence of the same phenomenon in dogs but further investigations with larger groups of dogs are needed to confirm this observation as a statistically significant relationship was not established.

A significant decrease ($P = 0.005$) in CSF albumin concentration (from 0.154 g/L to 0.147 g/L) was identified by nephelometry (but there was no significant difference found using high-resolution protein electrophoresis). The absence of any concurrent change in QAlb indicates that the difference in CSF albumin most likely reflects variations in serum albumin levels. This highlights the importance of using the QAlb ratio as the appropriate surrogate marker rather than CSF albumin concentration alone.

Paired high-resolution protein electrophoresis is recommended by the International Consensus Group for CSF Analysis (Reiber et al., 2003). Electrophoresis profiles with low albumin concentrations are frequently non-interpretable (Behr et al., 2006). Thanks to the microconcentration step we used, all electrophoresis profiles were interpretable even for albumin concentrations <20 mg/dL. High-resolution protein electrophoresis was shown to be a good method to estimate canine CSF albumin concentrations and represented an easy and readily available method.

CSF albumin values determined by high-resolution protein electrophoresis were lower than CSF values determined by nephelometry. In this study, CSF total protein concentration was measured by a colorimetric reaction with pyrogallol red. Although this technique is considered to have the greatest specificity (Marshall and Williams, 2000; Behr et al., 2003) it can underestimate CSF total protein in dogs because of its 20% lower affinity for globulin compared to albumin (Behr et al., 2003). This discrepancy could contribute to an underestimate in albumin values calculated by high-resolution protein electrophoresis. The loss of a small quantity of low molecular weight proteins during the microconcentration step could also contribute to the lower CSF albumin found by high-resolution protein electrophoresis. Further studies are required to determine the origin of the bias observed.

The mild increase in blood pH and decrease in blood Cl^- observed after omeprazole administration could be due to omeprazole-mediated inhibition of gastric acid and chloride secretion (Aichbichler et al., 1997). To the authors' knowledge, very little data concerning the effects of omeprazole on blood pH and Cl^- are available and further investigations are indicated to assess the clinical significance of these findings.

We also found a significant (although mild) increase in CSF Na^+ concentration after omeprazole administration. This finding is opposite to that expected in the context of a decrease in CSF production. Membrane transport mechanisms in the choroid plexus are similar to those in the renal tubule; CSF production depends on the active transport of Na^+ into the ventricles (Johanson et al., 2008). A decrease in uptake of Na^+ into CSF resulting in a reduction in CSF Na^+ concentration and a reduction of CSF production was demonstrated in dogs and rats treated with furosemide (Buhrley and Reed, 1972; Johnson et al., 1984). The importance of the minor CSF Na^+ concentration change in our study is unknown but would not support a reduction in CSF production.

Our study has several additional limitations. High-resolution protein electrophoresis was performed on samples that had been frozen whereas nephelometry was performed on cooled samples. However, as albumin has been demonstrated to be stable in frozen urine (–20 °C) for at least 24 months (Tencer et al., 1997), it is unlikely that the 1 month storage of CSF and plasma at –20 °C had a significant effect on albumin concentrations. It is also important to note that the study was performed on healthy dogs and it is possible that dogs with hydrocephalus or syringomyelia may respond differently. Further studies are required to assess the effects of omeprazole on dogs suffering from hydrocephalus or syringomyelia.

Conclusions

The lack of change in QAlb in the present study suggests that CSF production may not be affected following chronic oral therapy

with omeprazole in healthy dogs. Additional work is needed to assess the acute and chronic impact of omeprazole on CSF production in neurological patients suffering from conditions relating to CSF disturbance.

Conflict of interest statement

None of the authors of this paper have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Preliminary results were presented as an oral presentation at the 23th Annual ECVIM-CA Congress, Liverpool, 12–14 September 2013.

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