




Medical therapy using omeprazole in 12 hydrocephalic dogs: clinical, diagnostic, and therapeutic findings¹

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ABSTRACT.- Pelegrini L.F., Silva N.F., Campos O.P.S., Nery C.C., Silva F.M., Lemos R.S., Yamauchi K.C.I. & Amude A.M. 2019. **Medical therapy using omeprazole in 12 hydrocephalic dogs: clinical, diagnostic, and therapeutic findings.** *Pesquisa Veterinária Brasileira* 39(10):823-829. Setor de Clínica Médica de Pequenos Animais, Serviço de Neurologia Animal, Neurologia Clínica e Cirúrgica, Faculdade de Medicina Veterinária, Universidade de Cuiabá, Av. Beira Rio 3300, Cuiabá, MT 78065-420, Brazil. E-mail: amamude@hotmail.com

According to experimental studies with healthy dogs, omeprazole might decrease the CSF production by about 26%; therefore, book texts have been suggested the usage of omeprazole in medical protocols for hydrocephalus treatment. However, to the best knowledge of the authors, the usage and medical response of the omeprazole with substantial group of illness dogs, such as hydrocephalic animals, was lacking. This report describes clinical, diagnostic, and therapeutic findings in 12 dogs with hydrocephalus in which omeprazole were used for medical treatment. The diagnosis of hydrocephalus was accomplished by transcranial sonography (TCS) and/or computed tomography. The ventricular measurement was assessed periodically by TCS during medical treatment. Six dogs were diagnosed with non-obstructive hydrocephalus and in the other 6 cases hydrocephalus occurred with other concomitant anomalous encephalic disease often related with obstructive hydrocephalus, such as quadrigeminal cist, arachnoid cyst, chiary-like malformation, and syringomyelia. All of them had medical improvement after the use of omeprazole and the most of the cases had ventricular size reduction. In 10 dogs, the omeprazole was used as single drug, and in 2 dogs medical treatment with steroids and/or diuretics was previously being performed, and omeprazole was added because conventional treatment was resulting in mild to unsatisfactory medical control of the neurological status. The results of this paper shown that omeprazole may be used to ameliorate the neurological status in symptomatic hydrocephalic dogs. This work may represent the first description about the use of omeprazole in order to treat a substantial group of affected dogs with suspected increased intracranial pressure by hydrocephalus, probably due to limitation of CSF production.

INDEX TERMS: Medical therapy, omeprazole, hydrocephalus, dogs, clinic, diagnostic, therapeutic findings.

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RESUMO.- [Terapia médica utilizando omeprazol em 12 cães hidrocefálicos: achados clínicos, diagnósticos e terapêuticos.] O omeprazol diminui a produção do fluido cerebrospinal (FCE) por cerca de 26% de acordo com estudos experimentais em cães saudáveis. Segundo o conhecimento dos autores, embora utilizado na prática clínica e recomendado em livros textos, não há até o momento estudos clínicos em um grupo substancial de animais avaliando a resposta terapêutica ao uso do omeprazol em pacientes enfermos, tais como cães hidrocefálicos sintomáticos. Este trabalho descreve os achados clínicos, diagnósticos e terapêuticos em 12 cães com hidrocefalia que foram submetidos ao tratamento com omeprazol para o manejo médico de hidrocefalia. O diagnóstico de hidrocefalia e doenças neurológicas concomitantes foi realizado por ultrassonografia transcraniana (USTC) e/ou tomografia

computadorizada. A mensuração do tamanho ventricular foi realizada pela USTC durante o tratamento médico. Seis cães foram diagnosticados com hidrocefalia não obstrutiva e os outros 6 casos apresentaram hidrocefalia concomitante com outras afecções encefálicas anômalas comumente associada à hidrocefalia obstrutiva, tal como cisto quadrigêmio, cisto aracnóide, síndrome de *chiari-like* e seringomegalia. Em 10 cães o omeprazol foi utilizado como droga única e em 2 cães a terapia inicial foi a convencional utilizando esteroides e diuréticos, e o omeprazol foi adicionado, pois a resposta clínica a terapia convencional foi insatisfatória. Todos os animais obtiveram melhora dos parâmetros neurológicos e a maioria teve uma redução do tamanho ventricular após o uso do omeprazol. Os resultados deste estudo demonstram que o omeprazol pode ser utilizado para melhorar o estado neurológico em cães com hidrocefalia. Este estudo representa a primeira descrição clínica usando o omeprazol para tratar uma série de cães com suspeita de aumento da pressão intracraniana devido à hidrocefalia, provavelmente pela capacidade do fármaco em limitar a produção do FCE.

TERMOS DE INDEXAÇÃO: Terapia, omeprazol, hidrocefalia, cão, clínica, diagnóstico.

INTRODUCTION

Hydrocephalus is a condition involving an increase in the volume of the cerebrospinal fluid (CSF) with abnormal dilatation of the ventricular system within the cranium and consecutive destruction and atrophy of surrounding nervous tissue of the brain. The choice of treatment is generally dictated by the physical status, the age of the animal, and the cause of the hydrocephalus (Thomas 2010, Estey 2016). Ventricle-peritoneal shunts have been commonly used to divert the flow of CSF from the ventricles of the brain to the peritoneal cavity in human patients with hydrocephalus, and have proved to be an effective surgical treatment for hydrocephalus in dogs and cats (Kim et al. 2006, Kitagawa et al. 2008, Schmidt et al. 2019). Surgery does not decrease the damage to the nervous tissue secondary to the increased intracranial pressure (ICP) that have already occurred at the moment of diagnosis; in addition, surgery might be indicated with criteria because of the risk of the anesthesia, the risk of neurological and systemic complications intraoperative, and the risk of postoperative complications of shunt placement (Platt & Olby 2004, Dewey 2008, Gradner et al. 2019). No significant differences have been noted in clinical or imaging findings between surgically and medically treated dogs (Gillespie et al. 2019). In addition, ventricle-peritoneal shunts have an elevated cost, limiting this surgery for hydrocephalus treatment by many owners. Therefore, medical treatment has been commonly used to manage ICP in dogs with hydrocephalus (Platt & Olby 2004, Dewey 2008, Thomas 2010, Gillespie et al. 2019).

Medical treatment of hydrocephalus includes general supportive care and the administration of medications to restrict the production of cerebrospinal fluid and hence reduce the ICP. Angiotensin II plays an important role in regulation of blood flow to the choroid plexus and decreases the rate of production of CSF in rabbits and rats (Maktabi et al. 1990, 1993, Chodowski et al. 1995). Ethanol at a concentration of 150mg/dl (far below lethal levels) is one of the most potent inhibitory drugs for decreasing CSF production in dogs (Javaheri

& Corbett 1998). However, therapeutic uses of these drugs to treat hydrocephalus in dogs are not available.

Different medications has been traditionally used with this propose such as steroids (glucocorticoids), furosemide, mannitol, and carbonic anhydrase blockers (acetazolamide) (Sahar & Tsipstein 1978, Pollay et al. 1983, Platt & Olby 2004, Dewey 2008, Kim et al. 2009, Park et al. 2009, Estey 2016). Furosemide and acetazolamide may decrease the CSF production. The primary mechanism of action for various types of glucocorticoids is to decrease cerebrospinal fluid production; prednisone is the drug of choice and dexamethasone sodium phosphate has also been used to treat hydrocephalus, but long-term use should be avoided because of the higher incidence of side effects (Platt & Olby 2004, Dewey 2008, Thomas 2010, Estey 2016). Mannitol has been used mainly in cases of rapidly decompensating hydrocephalus (Thomas 2010), due its osmotic gradient (Pollay et al. 1983) and may be not used as on a daily basis therapy (Estey 2016).

Many of the drugs used to treat hydrocephalus (furosemide, mannitol, and carbonic anhydrase blockers) have diuretic activity, and caution must be exerted when using any drug with diuretic activity because electrolyte depletion is a common sequel; in addition, electrolyte loss is accelerated when diuretics are used in combination with steroids (glucocorticoids). Acetazolamide combined with glucocorticoids may cause potassium depletion at the therapeutic drug concentration, which often requires discontinuation of acetazolamide (Platt & Olby 2004, Dewey 2008, Thomas 2010, Estey 2016).

Experimentally, omeprazole was already proved to reduce ICP by decreasing cerebrospinal fluid production in healthy rabbits (Lindvall-Axelsson et al. 1992) and dogs (Javaheri et al. 1997). The authors have already used omeprazole added to steroid therapy (prednisone) in order to alleviate the increased ICP and ameliorate the neurological status in a naturally ill dog with congenital hydrocephalus unresponsive to conventional medical therapy (Amude et al. 2013). However, the description about the usage of the omeprazole in order to treat a substantial group of affected dogs with suspected increased intracranial pressure by hydrocephalus is lacking. Accordingly, the aim of this paper was to present the results of a series of cases in which omeprazole was used for the medical management of hydrocephalus.

MATERIALS AND METHODS

This work revised the medical records of dogs with neurological deficits suggestive of prosencephalic dysfunction alone or in combination with other nervous signs in which the neurological diagnostic approach suggested hydrocephalus as presumptive diagnosis. All cases were assisted at the Veterinary Teaching Hospital from "Universidade de Cuiabá" (2011-2013) and medical follow up were performed by neurological service of the Hospital.

In all cases, hydrocephalus was diagnosed by clinical signs, neurological and physical exam, and ultrasonography of the brain (transcranial sonography - TCS) through open fontanelles and/or temporal window, as well as through foramen magnum window (Carvalho et al. 2007, Cintra et al. 2014). In addition to the TCS, in some cases, computed tomography (CT) was also performed to diagnose hydrocephalus and/or concomitant anomalous disease, when additional imaging was recommended to accomplish the final diagnose. CT was carried out with a one channel helical tomography (Toshiba Xvision EX).

Hematological/biochemical evaluation, thoracic ray x, abdominal sonography, and cerebrospinal fluid (CSF) examination (lumbar puncture) were also performed in order to exclude asymptomatic subclinical hydrocephalus concomitant with systemic disease or other causes of encephalopathy as the cause of the neurological presentation. All animals were tested for canine distemper virus (CDV) antigen in CSF by rapid immunochromatographic test (Antigen Rapid CDV Ag Test Kit; Animal Genetics).

Omeprazole was used alone or in combination at the dose of 10mg/kg PO SID as previously described (Dewey 2008, Amude et al. 2013). When the animal was admitted to the Veterinary Teaching Hospital and no other medical management of hydrocephalus was previously started, the omeprazole was instituted as the unique drug in order to attempt medical treatment. When the animal was admitted with descompensated hydrocephalus in which conventional medical treatment (steroids and/or diuretics) had already being started previously, omeprazole was also added to the conventional medical treatment. The clinical response to medical treatment was scored subjectively as satisfactory (mild, moderate and optimal) or unsatisfactory.

The animals were followed up and transcranial sonography was performed through the period of clinical monitoring in order to assess the ventricular length during omeprazole therapy.

RESULTS

All dogs admitted by the neurological service though the period from 2011 to 2013 had the medical records revised, and 12 dogs were screened for this description since filled the criteria of the study; 6 dogs were diagnosed with non-obstructive hydrocephalus and in the other 6 cases hydrocephalus occurred with other concomitant anomalous encephalic disease often related with obstructive hydrocephalus (quadrigeminal cist - 1, arachnoid cyst - 1, chiary-like malformation - 3, and syringomyelia - 1). All of them had medical improvement after the use of omeprazole. In 10 dogs the omeprazole was used as single drug and showed optimal (n=8) to moderate clinical response (n=2). In 2 dogs medical treatment with steroids and/or diuretics had already been performed with mild to unsatisfactory medical control of the prosencephalic signs, however with the addition of omeprazole to the treatment they had improvement of the neurological status. The dog number, breed, neurological findings, diagnostic findings through imaginologic approach (TCS and/or CT), medical treatment (omeprazole singly or in addition with other drugs), response to therapy, ventricular size before and after omeprazole therapy, and time of clinical follow up were presented at Table 1. Six dogs had died during the follow up. Five died from non-neurological deterioration (respiratory failure, head trauma, acute not-known dead) and one dog died due to progressive neurological deterioration besides initial good response to the medical treatment.

The prosencephalic signs verified were characterized by circling, inappropriate consciousness content (behavioral change varying from fear to aggressiveness), compulsive walking, excessive vocalization, postural reactions deficits with normal to increased spinal reflex. Cranial nerves deficits were absent in the dogs with pure forebrain signs except bilateral absence of menace response (with normal fotomotor reflex). Divergent strabismus was also verified in one instance. Bilateral divergent strabismus, a common sign of hydrocephalus, was only verified in one dog presented

with the typical prosencephalic signs of the disease due to impairment of the third cranial nerve rather than cranium/orbita malformation due to hydrocephalus, since the strabismus was no more verified after one week of omeprazole therapy.

Rombencephalic signs (vestibular and/or cerebellar deficits) were verified in two instances concomitants to the prosencephalic signs; all of these dogs had hydrocephalus with concomitant neurological disease (quadrigeminal cist - 1, chiary-like malformation - 1). In two cases, rombencephalic signs (vestibular and cerebellar deficits) were the only nervous deficits, although hydrocephalus was recognized at imaginologic approach; such dogs were diagnosed with chiary-like malformation and concomitant hydrocephalus. Vestibular signs were characterized in these dogs by head tilt and/or positional strabismus; in addition, two dogs had rolling and tetraparesis. Cerebellar deficits were characterized by cerebellar ataxia (hypermetria with truncal and head ataxia) in one case, and hipermetria of the fore limb manifested during hopping test in the other three cases in which romboencephalic signs were recognized.

Hematological/biochemical evaluation, thoracic ray X, abdominal sonography, and CSF examination of all cases were within normal limits. Trauma was not suggested by the anamnesis, and the physical and laboratorial evaluations not showed any systemic abnormality. CDV antigen was not detected in CSF in any of the included dogs.

DISCUSSION

The importance of this report is the therapeutic use of omeprazole to ameliorate neurological signs in naturally affected dogs with hydrocephalus. Experimentally omeprazole was already proved to reduce ICP by decreasing the production of CSF in healthy rabbits (Lindvall-Axelsson et al. 1992) and dogs (Javaheri et al. 1997). The use of omeprazole for the treatment of hydrocephalus and syringomyelia in dogs has been suggested within the veterinary literature (Rusbridge et al. 2006, Dewey 2008, Thomas 2010, Estey 2016), and has being used by medical routine. The authors had already used omeprazole added to steroid therapy (prednisone) in order to ameliorate the neurological status in a naturally ill dog with congenital hydrocephalus unresponsive to conventional medical therapy (Amude et al. 2013). However, the use and effectiveness of omeprazole in clinical trials with naturally affected hydrocephalic dogs are lacking (Rusbridge et al. 2006, Thomas 2010, Estey 2016). To the best knowledge of the authors there are no description about the use of omeprazole in order to treat a substantial group of affected dogs with suspected increased intracranial pressure by hydrocephalus available within the scientific medical databases⁷.

Omeprazole, a specific inhibitor of H(+)-K(+)-activated ATPase (proton-pump inhibitor), has a dose-dependent inhibition of CSF production as determined by cerebroventriculocisternal perfusions in the rabbit; the reduction was 25% after an intravenous dose of 0.2 mg/kg of omeprazole (Lindvall-Axelsson et al. 1992). Initially the effect of omeprazole was thought to be due to the K(+)-H(+)-ATPase activity; however the effect is independent of the K(+)-H(+)-ATPase activity, since Sch 28080 - a potent inhibitor of H(+)-K(+)-ATPase - which is

⁷ PubMed-NCBI <<http://www.ncbi.nlm.nih.gov/pubmed/>>, Scholar Google <<http://scholar.google.com.br/>>, SciELO <<http://www.scielo.org/php/index.php>>

Table 1. Distribution of the dogs, with final diagnosis, clinical data, ventricular measure, response to hydrocephalus treatment and time of clinical follow up

Dog	Age at presentation	Diagnosis	Clinical signs at the hospital presentation	Conventional medical treatment before omeprazole treatment	Degree of clinical response after conventional medical treatment	Length of the ventricles before omeprazole treatment (cm)	Length of the ventricles after omeprazole treatment (cm)	Degree of clinical response after omeprazole treatment	Time of clinical follow up
1 - Pinscher	50 days	Congenital hydrocephalus	Severe prosencephalic signs, blindness, bilateral ventrolateral strabismus	Corticosteroid (prednisone)	Mild response that deteriorate after 3 weeks	NA	NA	Satisfactory (moderate)	Six months (natural death)
2 - Shit-zu	2 years	Obstructive hydrocephalus and quadrigeminal cyst	Severe prosencephalic signs, central vestibular signs, tetraparesis and neuropathic pain (cervical)	NP	-	RLV-3.3 LLV-3.3 TV - NV	NP	Satisfactory (moderate)	Two week (death during immediate pos chirurgical to craniotomy and ventriculoperitoneal shunt)
3 - Pincher	6 months	Congenital hydrocephalus	Severe prosencephalic signs and neuropathic pain (cervical)	Corticosteroid (prednisone) Diuretic (furosemide)	Unsatisfactory	RLV-2.67 LLV-2.52 TV - NV	RLV-3.63 LLV-3.93 TV - NV	Satisfactory (mild)	One year (death with neurological deterioration due to progression of the hydrocephalus)
4 - Pinscher	5 months	Obstructive hydrocephalus and quadrigeminal cyst	Moderate prosencephalic signs and neuropathic pain (cervical)	NP	-	RLV - 1.1 LLV - 0.3 TV - NV	RLV - 0.6 LLV - 0.3 TV - NV	Satisfactory (optimal)	Seven months (died of cranial trauma unresponsive to medical treatment)
5 - Pinscher	2 years	Congenital hydrocephalus	Moderate prosencephalic signs and neuropathic pain (cervical)	NP	-	RLV-0.93 LLV-1.01 TV - 0.34x0.24	RLV - 0.6 LLV - 0.7 TV - 0.2x0.2	Satisfactory (optimal)	Two years and 3 months
6 - Poodle	Two month	Congenital hydrocephalus	Moderate prosencephalic signs	NP	-	NA	NA	Satisfactory (optimal)	Five years (died of respiratory failure because of traqueal collapse)
7 - Pinscher	54 days	Hydrocephalus and Chiari-like malformation and syringohidromielia	Moderate prosencephalic signs	NP	-	RLV - 1.2 LLV - 1.3 TV - NV	RLV - 0.9 LLV - 1.02 TV - NV	Satisfactory (optimal) during 3 months followed by Satisfactory (moderate)	Two years

Medical response: unsatisfactory or satisfactory (mild, moderate, optimal). Satisfactory: optimal = animal became clinical normal free of neurological signs, moderate = animal improved the neurological status, many of the nervous signs became absent but with persisted with some residual neurological signs, mild = animal improved the neurological status however persisted with all the signs previously registered at the beginning of the presentation; NA = not available, NP = not performed, NV= not verified, RLV = right lateral ventricle, LLV = left lateral ventricle, TV = third ventricle.

Table 1. Continued...

Dog	Age at presentation	Diagnosis	Clinical signs at the hospital presentation	Conventional medical treatment before omeprazole treatment	Degree of clinical response after conventional medical treatment	Length of the ventricles before omeprazole treatment (cm)	Length of the ventricles after omeprazole treatment (cm)	Degree of clinical response after omeprazole treatment	Time of clinical follow up
8 - Maltes	3 years	Hydrocephalus and Chiari-like malformation	Proencephalic signs, blindness, mild vestibular signs (head tilt and positional strabismus) and cerebellar signs (hipermetria of left forelimb)	NP	-	RLV - 0.9 LLV - 1.0 TV - 0.49x0.42	RLV - 0.63 LLV - 0.79 TV - 0.4x0.4	Satisfactory (optimal) for one moth followed by satisfactory (moderate) for four month and satisfactory (mild)	One year
9 - Yorkshire	20 days	Congenital hydrocephalus	Proencephalic signs, inadequate grow rate	NP	-	RLV-0.28 LLV-0.32 TV - NV	NP	Satisfactory (optimal) until acute repentine death	Two months (acute repentine death)
10 - Rottweiler	30 days	Congenital hydrocephalus	Proencephalic signs, inadequate grow rate	NP	-	RLV-0.72 LLV-0.59 TV - 0.26x0.3	NP	Satisfactory (optimal) until acute repentine death	One month (acute repentine death)
11 - Yorkshire	5 years	Hydrocephalus Chiari-like malformation	Vestibular signs (head tilt, positional strabismus, circling) and cerebellar signs (hipermetria of left forelimb)	NP	-	RLV-0.74 LLV-0.79 TV - 0.36x0.36	NP	Satisfactory (moderate)	Eight months
12 - Poodle	1 year and 7 months	Hydrocephalus Chiari-like malformation	Vestibular signs (head tilt, positional strabismus, circling/rolling)	NP	-	RLV - 1.0 LLV - 1.2 TV - NV	NP	Satisfactory (optimal)	One year and two months

Medical response: unsatisfactory or satisfactory (mild, moderate, optimal). Satisfactory: optimal = animal became clinical normal free of neurological signs, moderate = animal improved the neurological status, many of the nervous signs became absent but with persisted with some residual neurological signs, mild = animal improved the neurological status however persisted with all the signs previously registered at the beginning of the presentation; NA = not available, NP = not performed, NV = not verified, RLV = right lateral ventricle, LLV = left lateral ventricle, TV = third ventricle.

more potent than omeprazole did not significantly affect CSF production (Javaheri et al. 1997). In addition to the studies with rabbits, experimental studies in canine model also suggested that omeprazole may decrease CSF production by about 26% (Javaheri et al. 1997).

These previous studies were carried out with healthy animals without increased ICP, and the extrapolation of those preliminary results for clinical usage of omeprazole in situations where the limited CSF production should be beneficial, such as hydrocephalus, might be done with caution. In order to check this, the application of omeprazole should be tested in ill dogs in which the limitation of CSF could ameliorate the signs of the disease, such as the 12 hydrocephalic dogs presented herein. The present description shown that the animals had not only clinical improvement, as well had reduction of the ventricular size.

Girod et al. (2016) suggested that CSF production in healthy dogs may not be affected by chronic oral therapy with omeprazole at the dose of 1.2mg/kg, differing from the previous results where administration of omeprazole by ventriculo-cisternal perfusion or intravenously shown to decrease CSF production in healthy dogs and rabbits (Lindvall-Axelsson et al. 1992, Javaheri et al. 1997). The difference of these results might be in part due to the administration route or the method employed to quantify the decrease of CSF production; while Lindvall-Axelsson et al. (1992) and Javaheri et al. (1997) had quantified by open system and canulation of CSF flow, Girod et al. (2016) had measured by albumin quotient determination in CSF samples. However, in the presented clinical description, at the dose of 10mg/kg, oral omeprazole could improve the neurological status of the hydrocephalic dogs, probable due to limiting the CSF production, since the most of the cases had ventricular size reduction after omeprazole therapy. Prospective studies in naturally affected dogs have been carried out by the authors in order to clarify the therapeutic use of omeprazole in other diseases that naturally course with increased ICP such as tumors and head trauma.

CONCLUSIONS

The results of this study shown that in naturally affected dogs with hydrocephalus, omeprazole may be used orally at the dose of 10mg/kg in order to and ameliorate the neurological status. Furthermore, the results suggested that omeprazole can be used in cases other than only congenital non-obstructive hydrocephalus including quadrigeminal cist, arachnoid cyst, chiary-like malformation, and syringomyelia, even when affected dogs are presented with only rombocephalic signs without prosencephalic deficits.

This work may represent the first clinical description using omeprazole in order to treat a substantial group of affected dogs with suspected increased intracranial pressure by hydrocephalus.

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