Torsemide: A Comprehensive Review

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INTRODUCTION

Torsemide (1-isopropyl-3-{[4-(3-methyl-phenylamino)pyridine]-3-sulfonyl} urea), a lipophilic anilinopyrimidine sulfonylurea derivative and one of the high-ceiling loop diuretics, is effective in the treatment of both acute and chronic congestive heart failure (HF). Its mechanism of diuretic action is blockade of the $Na^+/K^+/2Cl^-$ co-transporter in the thick ascending loop of Henle. Despite its similar site of action to other loops diuretics (e.g., furosemide), torsemide it not structurally related. Torsemide's unique chemical structure is responsible for its pharmacokinetic/pharmacodynamic properties, including: a long half-life, antifibrotic effects, potassium sparing effects, and anti-aldosterone/mineralocorticoid effects. Torsemide has been evaluated in murine and canine models of heart disease (failure) as well as spontaneous HF in humans, dogs, cats and horses. Given the potential beneficial effects of torsemide and unique pharmacokinetic properties a comprehensive understanding of this drug and its current and potential clinical uses is essential.

PHARMACOKINETICS AND PRECLINICAL STUDIES

Veterinary

Dogs: Intravenous torsemide reaches peak serum concentration 2–5 minutes after administration with a half-life of 120 minutes. The peak diuretic effect is observed 20–25 minutes after administration and the diuretic action persists for >90 minutes and has a lower urinary excretion rate compared with furosemide ($CL_{R\text{-}torsemide}$=0.38 mL min^{-1}, $CL_{R\text{-}furosemide}$=63.5 mL min^{-1}). This suggests that the diuretic profile of torsemide depends on its slower urinary excretion rate. After oral administration, the diuretic effect of torsemide begins within 20 minutes, peaks at 2 hours, and lasts for approximately 12 hours with a bioavailability of 80–100%. Torsemide is at least 10 times more potent than furosemide. Additional potential favorable properties of torsemide include significantly less kaliuresis compared with furosemide at equipotent doses, vasodilatory and coronary protective effects, and myocardial antifibrotic effects. Finally, despite the existence of a diuretic tolerance phenomenon well described after acute and repeated daily administration of furosemide, this response has not been observed after repeated administration of torsemide.

Cats: after oral administration, the diuretic effect of torsemide peaks at 4 hours and persists for 12 hours. Compared with furosemide, torsemide produces a significantly greater 24-hour sodium and potassium urinary excretion and greater overall urine volume. The diuretic effect of torsemide is approximately 10 times greater than furosemide in cats. Chronic oral and intravenous administration of torsemide in cats has not been evaluated.

Horses: after oral administration, torsemide reaches peak serum concentration at 3 hours and has a half-life of approximately 9 hours. Oral administration of torsemide results in a significant increase in urine volume and decrease in urine specific gravity. A direct comparison with furosemide and torsemide has not been performed in this species and therefore the relatively potency of torsemide is unknown in horses.

Torsemide has been shown to inhibit aldosterone receptor binding in the cytoplasmic fraction of the kidney in rats and has been hypothesized to confer its antifibrotic effects via this mineralocorticoid receptor blockade in the heart as well. Several studies in humans and rats have demonstrated significant differences in myocardial fibrosis in torsemide-treated patients compared with furosemide and spironolactone. However, a recent study in human patients with HF secondary to ischemic cardiomyopathy demonstrated that torsemide does not act as a mineralocorticoid receptor antagonist as previously reported. Rather, torsemide decreases the expression of lysyl oxidase and collagen cross-linking, both of which strongly correlate with parameters of myocardial fibrosis and ventricular chamber stiffness. While the exact etiology of torsemide's antifibrotic effects are debated, it remains clear that torsemide is superior to furosemide and spironolactone at reducing or reversing myocardial fibrosis in human patients with chronic HF secondary to ischemic and other cardiomyopathies.

Clinical Studies

Until recently in veterinary and human cardiology, torsemide has been exclusively utilized a second-line (rescue) diuretic to furosemide for the treatment of HF. Despite the fact that there are few to no data showing that furosemide is superior to other loop diuretics, it is clearly the first choice among the class, and it was the only loop diuretic in the top 200 most frequently prescribed drugs for humans in the US in 2008. Furthermore, furosemide was the first loop diuretic approved by the Food and Drug Administration in 1966 with torsemide not gaining approval 1993. By this time, furosemide was available in generic form and was firmly established as the first-line therapy. All loop diuretics are currently available in generic form with minor cost differences (e.g., furosemide $4/30 day or $10/90 day; torsemide $4/30 day or $15/90 day).

Human

Diuretic selection is largely dependent on physician preference. Current American Heart Association guidelines for the management of HF stress, that all patients who have evidence of cardiogenic fluid retention should be started on a loop diuretic. The guideline states that furosemide is the most commonly used diuretic for the treatment of HF, but some patients respond more favorable to torsemide because of the increased bioavailability. The guidelines do not expressly state that furosemide must be the first-line choice loop diuretic; however, current prescribing practices indicate furosemide remains the most commonly used loop-diuretic. A recent meta-analysis of relevant clinical trials comparing torsemide and furosemide in people concluded that torsemide significantly decreases HF and cardiovascular readmission compared with furosemide with no significant increase in adverse events. Clear and unequivocal differences in mortality have not been demonstrated.

Kasama *et al*. performed a 6-month, randomized trial in 40 patients with non-ischemic congestive HF and systolic dysfunction to assess the effects of torsemide and furosemide on cardiac sympathetic nerve activation. All patients were initiated on angiotensin-converting enzyme (ACE) inhibitors, and half of the patients were also receiving beta-blockers. Baseline characteristics did not differ between the 2 groups. Mean doses of torsemide and furosemide used were 6.8 mg and 33 mg, respectively. Results demonstrated that, left-ventricular end-diastolic and systolic volumes, and brain natriuretic peptide (BNP) levels significantly reduced ($p<0.001$) in patients receiving torsemide, but not furosemide. Left-ventricular ejection fraction did not differ from baseline in either group. New York Heart Association (NYHA Table 1) functional classification improved significantly in both groups; however, NYHA class was

better in the torsemide group. The investigators concluded that compared with furosemide, torsemide decreases cardiac sympathetic nerve activation and left-ventricular remodeling.

Table 1. New York Heart Association (NYHA) classification

Class I	No limitation. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitation (asymptomatic LV dysfunction).
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pectoris (mild CHF).
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).

The neurohumoral effects of furosemide and torsemide were compared in another human trial. In this 6-month, open-label, parallel-group, crossover study of 50 patients with chronic stable HF secondary to hypertensive heart disease, aortic insufficiency, non-ischemic dilated cardiomyopathy, or old myocardial infarction (NYHA class II or III), patients were randomized to receive either their current furosemide dose (20–40 mg) or torsemide (4–8 mg). All patients included were receiving ACE inhibitors. Beta-blocker therapy was given for at least 1 year and other therapies were given for at least 6 months prior to enrollment. Baseline demographics were similar between the 2 groups. At 6 months, neurohumoral parameters were unchanged in the furosemide group; however, patients randomized to receive torsemide had significantly lower left-ventricular end-diastolic diameter, left-ventricular mass index, BNP levels, with improved Doppler filling parameters, and increased plasma renin and aldosterone levels. An increase in circulating aldosterone is thought to be the result of torsemide preventing circulating aldosterone from binding to its receptor and therefore remaining in circulation. In this study, an increase in plasma aldosterone positively correlated with improvements in left ventricular dimensions (reduction in LVDd) and diastolic function. Thus, this study suggests that oral torsemide attenuates myocardial remodeling and improves LV function by blocking aldosterone receptors in patient with HF. Additionally, patients who received a higher dose of torsemide had more improvement in parameters than the low dose torsemide group, suggesting the presence of a dose-dependent relationship. Therefore, the authors concluded that switching from furosemide to the higher-dose of torsemide improved parameters that may be associated with improved outcomes in patients with HF secondary to these conditions.

In 2002, results of the torsemide in chronic HF study (TORIC) were published. The objective of this study was to investigate the safety, tolerability and efficacy of torsemide in patients with HF secondary to any etiology excluding congenital heart disease, pericardial disease, or atrioventricular block compared with furosemide or other diuretics (spironolactone, amiloride, hydrochlorothiazide, indapamide, triamterene, and altizide,) in an open-label, non-randomized, post-marketing surveillance trial. Patients with NYHA class II–III HF received either diuretic therapy with torsemide orally (n=778), furosemide orally (n=527) or other diuretics (n=72) on top of their existing protocol (digoxin 52.6%, beta-blocker 9.5%, ACE inhibitor 32.3%) for 12 months. In addition to safety and tolerability, efficacy was assessed by documentation of mortality, morbidity, NYHA class, and serum potassium levels every 3 months. This study confirmed the safety and tolerability of torsemide in HF patients. Mortality was significantly lower in the torsemide (n=17, 2.2%) than in the furosemide/other diuretics group (n=27, 4.5%) (p=0.05). Improvement in NYHA class, was observed in more patients who received furosemide or torsemide (n=356, 45.8%) than those who received furosemide/other

diuretics (n=223, 37.2%) (p=0.00017). At the end of the study, abnormally low serum potassium levels were observed in fewer torsemide (n=95, 12.9%) than furosemide/other diuretics patients (n=102, 17.9%) (p=0.013). The authors concluded that torsemide is safe and well tolerated in patients with HF secondary to a variety of cardiac conditions. Although not designed as a mortality study, TORIC suggested a lower mortality amongst HF patients treated with torsemide compared to furosemide/other diuretics. Functional improvement and a lower incidence of abnormal serum potassium levels were also observed in patients receiving torsemide as compared to those receiving furosemide/other diuretics. While this study shows promising results regarding the use of torsemide, a direct comparison to furosemide alone was not reported and represents a limitation of this study.

Veterinary

Three studies evaluating the utility of torsemide in veterinary species have been described. The first two studies are prospective, comparing the effects of torsemide and furosemide in dogs with HF secondary to myxomatous mitral valve disease (MMVD) and the third study is a retrospective study describing the use of torsemide in 17 cats with HF of unreported etiologies. A fourth manuscript describing a small (n=3) case series of torsemide used in dogs with advanced HF has also been published. In 2012, Peddle *et al*. described the effects of torsemide and furosemide on clinical, laboratory, radiographic, and quality of life (QOL) variables in dogs with HF secondary to MMVD. Seven client-owned dogs with stable HF secondary to MMVD already receiving furosemide, ACE inhibitor, and pimobendan were enrolled. Utilizing a double-blinded, randomized, crossover design, dogs were either administered oral furosemide at their current dose or an equivalent oral dose of torsemide (1/10 of the daily furosemide dose divided into twice daily dosing) on day 0. Crossover occurred at day 7 and the study ended on day 14. Clinical, laboratory, radiographic, and QOL variables were evaluated on days 0, 7 and 14. No dogs developed recurrent HF during the study. Mean furosemide dose on day 0 was 5.13 mg/kg/day (range 2.8–9.6). Following torsemide treatment, creatinine (p=0.020), urea nitrogen (p=0.013), phosphorus (p=0.032), albumin (p=0.019), carbon dioxide (p=0.015) and anion gap (p=0.005) were significantly increased, and urine specific gravity (p=0.004) and chloride (p=0.021) were significantly decreased compared with furosemide dosing. A table of results for each dog is not available for this study, therefore, the clinical significance of these differences cannot be determined. In addition, there were no differences in QOL. Results of this study indicate that torsemide is equivalent to furosemide at controlling clinical sign of HF in dogs and is likely to achieve greater diuresis compared with furosemide. While statistically significant changes in electrolytes, BUN, and creatinine were identified in the torsemide treated dogs, the changes were small and none of these variables were out of the normal reference range.

Chetboul *et al*. evaluated the short-term efficacy and safety of torsemide and furosemide in 366 dogs with HF secondary to MMVD (the TEST study). The TEST study was designed as a non-inferiority study to demonstrate that torsemide is not worse than furosemide (the reference control) in the treatment of congestive HF secondary to MMVD. The hypothesis of inferiority was defined by $H0: p_{torasemide} - p_{furosemide} \leq -20\%$. The study was prospective, randomized, single-blinded and reference-controlled with 3 months of follow-up. Dogs of all breeds, weighing >3 kg, were eligible for inclusion if they presented with current or previous episode of mild to severe HF secondary to MMVD. The primary efficacy criterion of the study was the percentage of dogs with treatment success defined as improved clinical and radiographic signs in dogs suffering from active congestive HF or maintenance of stable condition congestive HF in dogs without clinical or radiographic signs of congestive HF at enrollment. The secondary criterion was a composite cardiac endpoint; time to reach the composite cardiac endpoint defined as:

spontaneous cardiac death, euthanasia due to HF, or worsening modified NYHA class. Dogs that improved clinically but not radiographically (and vice versa) were considered as treatment failure. Adverse events were reported by clinical investigators during the course of the study and safety was assessed by occurrence of adverse events and changes in IRIS stage, creatinine, and potassium values over the study period. Enrolled dogs received either torsemide q24h (n=180) or furosemide q12h (n=186) in addition to standard HF therapy (ACE inhibitor, pimobendan, ± digoxin) for 3 months. The differences between the two groups at baseline included duration of heart disease (furosemide 247 days; torsemide 126 days) and severity of dyspnea (torsemide>furosemide). Despite patients in the furosemide group having a longer duration of heart disease prior to enrollment, there was no difference between groups regarding pretrial medications (furosemide, ACE inhibitor, pimobendan) and duration of treatment pretrial. However, there were relatively few first onset HF dogs in both groups (N=x or a %). Results of the TEST study demonstrated that torsemide was non-inferior (i.e., not less effective) than furosemide ($p_{torasemide} - p_{furosemide}$=+1%; 95% CI [-12%; +14%]). In addition, torsemide was associated with a 2-fold reduction in the risk of reaching the composite cardiac endpoint (adjusted HR=0.47; 95% CI=0.27–0.82; p=0.0077) as compared with furosemide. This study supports the use of once daily torsemide as an effective oral diuretic in dogs with HF secondary to MMVD receiving standard background therapy including: an ACE inhibitor and pimobendan. However, a non-inferiority study cannot address the important clinical question, is torsemide superior to furosemide in dogs with congestive HF secondary to MMVD. Lastly, because there were relatively few dogs with first onset congestive HF included in the study (30%) conclusions regarding this specific indication cannot be made.

Giatis *et al*. retrospectively evaluated the records of 17 client-owned cats switched from furosemide to torsemide due to uncontrolled, 3 or more instances of congestive HF within the preceding 10 weeks (n=6), or refractory HF , oral furosemide at >5.5 mg/kg/day (n=11). All cats were initially treated with oral furosemide and various concurrent cardiac therapies (ACE inhibitors, clopidogrel, pimobendan, atenolol, diltiazem, sotalol, hydrochlorothiazide, spironolactone, and potassium supplement). Median oral furosemide dose was 6.1 mg/kg/day (range 2.9–16.6 mg/kg/day) immediately before starting torsemide, and median initial oral torsemide dose was 0.7 mg/kg/day (range 0.4–1.6 mg/kg/day [furosemide dose equivalent =7 mg/kg/day]). Median duration of HF therapy before starting torsemide was 26 days (range 5–895 days). Median time to first recheck after starting torsemide was 8 days (range 2–27 days) with HF unimproved in 2 cats, improved in 6 cats, and resolved in 9 cats. Serum creatinine was higher (p=0.003), whereas K^+ (p=0.01) and Cl^- (p=0.002) were lower in patients at first recheck after starting torsemide. Median survival time for cats after starting torsemide was 87 days (range 3–466 days) with a median final torsemide dose of 1.0 mg/kg/day (range 0.2–2.2 mg/kg/day). During chronic therapy, torsemide dose was reduced in 3 cats because of azotemia. Mortality was due to death or euthanasia from refractory HF (n=10), sudden death (n=1), euthanasia due to pleural effusion of suspected neoplastic etiology (n=1), and euthanasia due to azotemia 230 days after starting torsemide (n=1). This study demonstrated that torsemide on background therapy helped extended chronic HF control in cats refractory to furosemide. While three cats did require dose reduction of torsemide related to worsening azotemia, only one cat was euthanized for this finding, 230 days after starting torsemide. Additional studies are needed to evaluate the long-term safety, efficacy, and superiority of torsemide compared with furosemide in cats with HF.

Future Directions

Human

Currently, patients are enrolling in a multicenter, randomized, open label, blinded endpoint phase-IV trial (TORNADO). The study plans to include 120 patients with HF excluding: acute coronary syndrome, hypertrophic cardiomyopathy, uncontrolled hypertension, and uncontrolled diabetes mellitus in NYHA functional class II–IV, treated with optimal loop diuretic therapy. At enrolment, patients are required to be stable and receiving a fixed dose of loop diuretics. Patients are randomized to treatment with furosemide or torsemide (randomization 1:1). After randomization, the current fixed dose of furosemide is continued or is replaced by an equipotential dose of torsemide (4:1) based on the manufacturer's recommended dosing. The study consists of two reevaluations (3 and 6 months after enrolment) with minimal follow-up after 6 months. Assessment involves clinical examination, QOL questionnaire, laboratory tests, echocardiography, electrocardiography, 24-hour Holter monitoring, 6-min walk test and assessment of fluid retention. In addition, any need for diuretic dose adjustment will also be recorded. The primary objective is to compare the effects of torsemide and furosemide on clinical and biochemical parameters of hemodynamic and neurohormonal compensation and myocardial remodeling. Secondary objectives include monitoring of: changes in signs and symptoms of HF, NYHA functional class, QOL, diuretic dosage adjustments, rate of hospital readmissions and mortality. This study was expected to conclude in late 2017 or early 2018.

Veterinary

Use of torsemide in veterinary practice continues to expand. Currently, UpCard® (torsemide 0.75, 3.0, and 7.5 mg tablets) is a commercially available veterinary product in the EU, licensed for the treatment of clinical signs of edema and effusion related to congestive HF in dogs. The recommended dose of UpCard® is 0.1 to 0.6 mg per kg bodyweight, once daily. Several short-term studies have contributed promising results and anecdotal usage of torsemide suggests that it is a highly effective loop diuretic in particular for dogs and cats that are refractory to standard therapy including high dose furosemide. While the pharmacokinetics of torsemide suggests once daily dosing may be adequate in dogs and cats with HF, anecdotal usage of this drug suggests that twice daily dosing is typically required to achieve the desired clinical outcomes in dogs and cats that are furosemide dependent. Treatment of first onset or early HF with torsemide has not been compared to furosemide and in this setting once per day dosing if effective, could be desirable by clients. In addition, the reported benefits of torsemide in comparison to furosemide in human patients with HF secondary to a myriad of etiologies warrants investigation in veterinary species. The reported benefits are multifactorial and in large part the result of torsemide's unique pharmacokinetic and antifibrotic properties. Well designed, adequately powered, randomized controlled clinical studies that evaluate efficacy and safety of torsemide in comparison to furosemide for the treatment of both first onset HF and refractory HF in dog and cats are needed to better elucidate its role in HF management.

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One Hundred and Thirty-Seven Years of Disc Disease: What We Know Now

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Introduction

The first report of an intervertebral disc herniation (IVDH) in the dog dates from 1881. Around that time several reports appeared that identified spinal cord compression by material located in the epidural space and ultimately connected it to the intervertebral disc, so called endochondrosis intervertebralis. Since then there has been a torrent of papers on this topic. Indeed, PubMed literature searches with the words intervertebral disc or disk and dog will find over a thousand peer reviewed papers. The importance of this topic relates to the frequency with which dogs suffer problems related to intervertebral disc degeneration (IVDD). It was estimated that there are 20,000 new cases of acute thoracolumbar intervertebral disc herniations (IVDH) presenting to surgeons in North America every year[1] and a lifetime prevalence of disc associated disease of approximately 3.5% across all dogs in an insurance based epidemiological study in the Netherlands.[2] There are clear breed predispositions to different forms of IVDD that speak to both genetic underpinnings of IVDD and to environmental influences in the type of activities different dog breeds participate in. Given the extensive literature, this review will focus on key changes in our understanding of IVDD and management of IVDH.

Intervertebral Disc Degeneration

Our understanding of IVDD has been strongly influenced by the seminal work done by Hansen in the 1950s.[3,4] In his detailed study of the pathology of IVDD, he described the degenerative process of the intervertebral disc and categorized his observations according to the age of onset and character of the pathology into type I and type II IVDD. It is worth noting that he did reference other authors who made similar observations before him. Hansen type I IVDD occurs in chondrodystrophoid breeds, involves early chondroid metaplasia of the nucleus pulposus (NP) due to replacement of the resident notochordal cells by cells with characteristics of chondrocytes. This is followed by cell death and calcification of the NP and occurs along the length of the vertebral column. Splitting of the annulus fibrosus (AF) results in extrusions (IVDE) of the degenerate NP into the vertebral canal. Hansen type II IVDD occurs in non-chondrodystrophoid breeds of dog, and occurs later in life at points of maximum mobility and stress in the vertebral column, without the calcification seen in type I IVDD. While the changes in the NP were termed fibroid metaplasia, Hansen's description is of a process of maturation in which there is dehydration of the nucleus pulposus with progressive collagenization associated with foci of degeneration and splitting and thickening of the AF. Subsequent papers that described and quantified changes in the chemistry of intervertebral discs as they degenerated are reviewed in detail.[5] More recently, this interpretation of Hansen's work has been called into question and pathological studies have suggested that in both types of IVDD there is replacement of notochordal cells with chondrocytes. The authors suggest the process should be called chondroid metaplasia.[6] Given the clear genetic predisposition of chondrodystrophoid breeds for early IVDD, it was only a matter of time until the mutation or mutations that drive this early degeneration were described. Short limb length is associated with an FGF4 retrogene on chromosome (CFA)18 but this variant was not associated with IVDE. However, using the Nova Scotia duck tolling retrievers, a breed that includes dogs with a range of limb lengths, an additional FGF4 retrogene was identified on CFA12. Presence of this retrogene conferred a 50-

fold increase in risk for IVDE, and quantitative PCR studies demonstrated dramatically elevated expression of the gene within the intervertebral disc. It is proposed that FGF4, a growth factor that is expressed at high levels in the developing limb buds and in the somites and notochord, is driving the premature degenerative process.[7] There is now a genetic test for this retrogene and selective breeding away from this deleterious trait may be possible in some breeds, but is challenging in breeds like the Dachshund that have an extremely high prevalence of the variant.

INTERVERTEBRAL DISC HERNIATION

The types of intervertebral disc herniation recognized clinically have expanded dramatically from the classic Hansen type I (acute) IVDE and Hansen type II (chronic) intervertebral disc protrusion (IVDP) with the advent of routine magnetic resonance imaging. The degeneration leading to Hansen's type I and II IVDH have been described in the pathology section and the only additional notes to add relate to the distribution of the disc material along the vertebral canal. Hansen's type I IVDE occurs most commonly, but not exclusively, in chondrodystrophoid breeds in the cervical region and then clustering around the thoracolumbar junction. Peak age of onset is from 3–6 years of age, although it can occur from 2 years to extreme old age. Degenerate, calcified NP can be extruded focally, in a button like shape, can extrude as a 'carpet' extending over many vertebrae or can be a combination of these 2 forms. The consequent spinal cord injury varies in severity and pathology, reflecting relative contributions of compression versus contusion. It is important to note that we can see a range of different combinations of acutely extruded calcified material that has become chronic, with an acute injury overlaid. We can also see Hansen type II protrusions with acute extrusions then occurring at the same site. A detailed summary of the spinal cord pathology seen with Hansen type I IVDE can be found in a recent white paper.[8] It is also important to note that a progressive hemorrhagic syndrome, progressive myelomalacia, can be initiated following Hansen type I IVDE and is characterized by intraparenchymal and subdural thrombosis and hemorrhage with neuronal necrosis. Hansen's type II protrusions are more common in the caudal cervical spine, frequently associated with more widespread degenerative changes of the spine in disc associated wobblers syndrome (DAWS), at the thoracolumbar junction and the lumbosacral junction. Chronic compression of the spinal cord results in mixed pathology affecting both grey and white matter with a picture of gradual neuronal loss and gliosis although there is a real lack of published histopathological data for this particular disease.

As anyone who works in the field of neurology knows, there are many more types of IVDH. First, there are extrusions of healthy, non-degenerate NP. These typically occur in active, young dogs during exercise. While numerous different names have been applied to these diseases over the last 2 decades, we are relaxing into naming terminology that describes the material extruded and whether it is compressive or not. As such, a dog may suffer from an acute compressive or non-compressive hydrated NP extrusion (ACNPE versus ANNPE).[9,10] The hydrated NP is extruded rapidly into the overlying vertebral canal causing an acute contusive spinal cord injury, frequently lateralized due to deviation of the disc material by the dorsal longitudinal ligament. The disc material may disperse, but can produce focal compression. It can also be extruded with such force that it penetrates the meninges and into the spinal cord parenchyma. It is worth mentioning fibrocartilaginous embolism (FCE) here. In this disorder hydrated NP is embolized within the vasculature and is likely a variation on ANNPE. Indeed, early reports of the pathology noted NP within the vasculature but also within the vertebral canal.[11] Variations on this theme include the interesting discussion around 'discal' cysts' which are most likely just a variation on ACNPE in which the NP has become liquefied.[12] Finally, disc

herniations can result from trauma. If the affected disc is healthy and hydrated, a syndrome like ANNPE or ACNPE occurs, but there can be a compressive lesion cause by AF or degenerate NP. In addition, the forces generated during a traumatic event can force disc material through the meninges and into the spinal cord. Less well defined at this time is the phenomenon of acute IVDE in chondrodystrophoid breeds of dog that are over the age of 10 years. In these dogs, degenerate NP can be acutely extruded as in Hansen type I IVDE but the nuclear material is not calcified. In larger breed dogs, it is not uncommon to encounter acute disc extrusions in which the compressive material includes a large fragment of annulus fibrosus. In addition, likely due to the relatively increased epidural space in these non-chondrodystrophoid dogs, there is extensive epidural hemorrhage, frequently resulting in multilevel hematomas.

Clinical Presentation

Our interpretation of the clinical presentation of dogs with IVDE has advanced in certain specific ways. Presenting clinical signs reflect the location and type of IVDH ranging from pain to paralysis. There are some important changes in the way we assess and interpret the neurological examination in dogs. First is the recognition of spinal shock. This phenomenon occurs following acute severe spinal cord injury and so is seen most commonly following ANNPE, ACNPE and FCE, and is associated with loss of reflexes in the immediate post injury period.[13] Recovery of the perineal, followed by the patellar reflex occurs within the first hour after injury typically, with slower recovery of the withdrawal reflex.[14,15] Second is the recognition of signs of progressive myelomalacia (PMM). This condition is a fatal complication of acute IVDE and if a very careful neurological examination is performed, clinical signs of a more extensive spinal cord lesion are present. These include a more cranial location of the cutaneous trunci reflex than expected, coupled with loss of the pelvic limb spinal reflexes and loss of abdominal tone.[16,17] Finally, there are a range of different clinical scales available to describe the presenting severity. The most basic of these categorizes the dog as walking or not, and these escalate in detail to more granular 12-point scales.[18,19] In the tables used below grade 2 is ambulatory paraparetic, 3 is non-ambulatory paraparetic, 4 is paraplegic with pain perception, and 5 is paraplegic with no pain perception.

Diagnosis and Management

There has been a big shift in the imaging diagnosis of IVDD away from myelography to computed tomography (CT) for calcified IVDE, CT myelography and, of course, to MRI. Indeed, most newly certified veterinary neurologists are far more comfortable with the interpretation of an MRI than any other imaging modality. While myelography and CT identify sites of compression and allow quantification of the severity of that compression, repeated studies on the relationship between compression and outcome have failed to find an association. By contrast, MRI can identify and quantify parenchymal damage, and longitudinal and cross-sectional extent of hyperintensity on T2 weighted images is associated with outcome in ANNPE as well as FCE and type I IVDE.[20,21] MRI has also allowed us to refine the diagnosis of hydrated NP extrusions.

There have been advances in predicting outcome in acute IVDE—the field is less clear for chronic IVDP. Firstly, examination of large numbers of clinical cases with well-defined IVDE has allowed the natural history of the disease to be documented. Secondly, while many CSF and imaging biomarkers have been evaluated, the addition of serum biomarkers such as GFAP and phosphorylated neurofilament heavy chain (pNF-H) is showing real promise at predicting recovery in dogs that present with no pain perception using practical serum measurements.[22,23]

Outcome numbers from a range of papers have been summarized in the following tables using conservative versus surgical management.[8]

Medical management of IVDD has not changed much over the last 50 years. The focus is on pain control, muscle relaxation, avoidance of new injury (strict rest), and rehabilitation. While there are publications on acupuncture in place of surgery, the data are not compelling. Adjunctive neuroprotective therapies for acute, severe spinal cord injuries have been investigated in placebo controlled clinical trials in dogs with IVDE and no therapy has convincingly shown benefit.[24-26] The use of mesenchymal stem cells as a neuroprotective, anti-inflammatory strategy does show promise, but more evidence of benefit is needed.

Surgical management of IVDD has not changed much although surgical equipment and approaches have evolved. This is particularly true of cervical IVDH, for which ventral slot decompression remains the most effective way to remove herniated disc material. Dorsal laminectomy and even a lateral approach may be used when the compressive material cannot be retrieved from the ventral approach. The surgical approach to thoracolumbar IVDH has evolved from dorsal, to hemilaminectomy, to more minimalist approaches such as a pediculectomy and finally to partial corpectomy, allowing a more ventral approach to chronic IVDH. The most burning questions for surgeons are which cases need surgery and how quickly. The following table summarizes data from the 1960s to the current day for acute thoracolumbar IVDE and suggests that non-ambulatory dogs with acute compressive lesions benefit from surgery.

Grade	**2**	**3**	**4**	**5**
Summary surgery	~100%	~100%	90%	58%
Summary fenestration	90%	90%	90%	35%
Summary conservative	75%		~50%	<10%

Timing of surgery is contentious with the majority of discussion revolving around whether there is a need for immediate surgery of a dog presenting with acute onset of paraplegia with no pain perception. While studies have failed to show a difference in outcome in these dogs based on timing of surgery[27] there is evidence that delaying surgery in these dogs is associated with development of progressive myelomalacia,[17] the other risk factors for this condition being severity of injury and IVDE involving the caudal lumbar discs[28].

Post-operative care has changed over the years and there is more focus on rehabilitation, and therapies such as cold laser and pulsed electromagnetic fields. Rehabilitation is especially important for severely injured dogs and for dogs with chronic (Type II) IVDH and the field of adaptive neurorehabilitation is expanding quickly.

THE FUTURE

The landscape around IVDD and IVDH is likely to change in the near future. The identification of the FGF4 retrogene as a cause of early chondroid metaplasia and degeneration can allow breeding strategies to reduce prevalence of this condition in chondrodystrophoid breeds. Minimally invasive surgical techniques are on the horizon and could improve our ability to treat type II IVDH in particular. Neuroprotective strategies will continue to evolve and, ultimately, we may be able to limit secondary tissue damage better. Finally the post injury rehabilitation of dogs is at the tipping point with new strategies emerging.

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