Risk factors associated with development of seizures after use of iohexol for myelography in dogs: 182 cases (1998)

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Objective—To determine prevalence of seizures after use of iohexol for myelography and identify associated risk factors in dogs.

Design—Retrospective study.

Animals—182 dogs that received iohexol for myelography in 1998.

Procedure—Medical records were reviewed for age, breed, sex, weight, dose and total volume of iohexol, injection site, number of injections, lesion type and location, total duration of anesthesia, duration from time of iohexol injection to recovery, presence and number of seizures, and whether surgery followed the myelogram.

Results—39 (21.4%) dogs had at least 1 generalized seizure during or after myelography. Injection site was strongly associated with prevalence of seizures, and risk of seizure was significantly higher after cerebellomedullary injections, compared with lumbar injections. Mean total volume of iohexol administered to dogs that had seizures was significantly higher, compared with that administered to dogs that did not have seizures, although dosage did not differ between groups. Weight was significantly correlated with risk of seizure, and dogs that weighed > 20 kg (44 lb) had higher prevalence of seizures than dogs that weighed < 20 kg.

Conclusions and Clinical Relevance—It is preferable to administer iohexol via the L5-6 intervertebral space to minimize the risk of seizures. Higher prevalence of seizures in large dogs, compared with smaller dogs, may be caused by administration of larger total volumes of contrast agent per volume of CSF. (J Am Vet Med Assoc 2002;220:1499-1502)

Myelography is a useful and generally safe diagnostic tool for the radiographic diagnosis of spinal cord disease in dogs. However, adverse effects associated with intrathecal injection of contrast media have been widely reported and include seizures, apnea, worsening of neurologic status, cardiac arrhythmias, and rarely, aseptic meningitis. Metrizamide, the first water-soluble nonion-ic contrast agent used for performing myelograms in domestic species, was reported to have substantial adverse effects associated with neurotoxicosis. Frequency of seizures in dogs after intrathecal administration of metrizamide was reported to range from 15 to 65% and was postulated to be related to weight, injection site, injection volume, and duration of anesthesia. Because of this high prevalence of complications, its use has largely been replaced by iohexol, a second generation nonionic radiologic contrast medium that is apparently less epileptogenic than metrizamide.

Development of postmyelographic seizures with iohexol has been reported to occur in 0 to 10% of dogs and, similar to metrizamide, has been associated with patient weight and injection site. Additional factors that reportedly influence the development of seizures include number of injections, receiving multiple cerebellomedullary injections, sex, and breed, with male dogs and Doberman Pinschers at higher risk, compared with females and other breeds. Caudal cervical spondylomyelopathy has also been associated with an increased prevalence of seizures. Anesthetic protocol does not influence seizure activity after iohexol or metrizamide administration, with the exception of phenothiazine derivatives, which increase prevalence of seizures.

At the Veterinary Teaching Hospital of the University of Pennsylvania (VHUP), our clinical impression was that the prevalence of seizures after administration of iohexol for myelography was higher than that reported in the veterinary literature. The purpose of this study was to determine the prevalence of seizures associated with myelography in our hospital and to identify associated risk factors. Our hypothesis was that large breeds, higher doses of contrast material, shorter anesthe sia times, and nonsurgical diseases were factors that would predispose dogs to develop seizures after myelography.

Criteria for Selection of Cases

Medical records of all dogs that underwent myelography with iohexol (240 mg of iodine/ml) at VHUP from January 1998 to December 1998 were evaluated. Dogs with a history of prior seizure activity, those that were euthanatized prior to recovery, and those with > 1 myelogram during the study period were excluded.

Procedures

Data acquisition—Age, breed, sex, weight in kilograms, dose and volume of contrast agent, injection site, number of injections, duration of anesthesia, duration from time of injection of contrast medium to recovery, presence of seizures, number of seizures, and whether or not surgery immediately followed the myelogram were recorded. Duration of anesthesia was defined as the time from intubation to extubation. Cases were defined as dogs that developed seizures, whereas controls did not. Anesthetic protocols varied among patients. Most
patients received glycopyrrolate or atropine and an opioid (often hydromorphone) before induction of anesthesia. Anesthesia was induced with thiopental at 2 to 4 mg/kg (1 to 2 mg/lb) to effect and maintained with isoflurane inhalant. Phenothiazine derivatives were not used in any of these patients. All patients received IV fluid therapy during the myelogram consisting of either lactated Ringer’s solution or a nutritional fluid supplement at a rate of 5 to 10 ml/kg/h (2.3 to 4.5 ml/lb/h). Seizures were defined as episodes characterized by the following: excessive salivation, chewing movements, rigid extension of the limbs, clonic limb activity or pallidling, uncontrollable jerking of the head and trunk, and urinary or fecal incontinence. Seizures were observed and recorded by a variety of people including anesthesiologists, anesthesia technicians, neurologists, interns, and fourth-year veterinary students. Cerebrospinal fluid analysis was not one of the parameters evaluated in this study.

Lesion types were also recorded and classified as intervertebral disc disease, caudal cervical spondylomyelopathy, other extradural compressive disease (eg, vertebral malformation, extradural tumors), and intramedullary disease (eg, presumptive fibrocartilaginous myelopathy, granulomatous meningoencephalomyelitis, neoplasia, degenerative myelopathy). Lesion location was recorded and allocated into the following groups: C1-C5, C5-C6, C6-T2, T3-L3, L4-S1. Dogs with lesions that did not fit into 1 of these groups were recorded separately.

Statistical analysis—Variables (eg, dose and volume of iohexol, injection site, total duration of anesthesia) were compared between dogs that did and did not develop seizures. To test for differences between these 2 groups for continuous data, the Student t-test was used. Categoric data were analyzed by use of a χ² or Fisher exact test.

Multivariate analyses were performed by use of logistic regression. A value of P < 0.05 was considered significant. All data were analyzed by use of statistical software.

Results

One hundred eighty-two dogs were evaluated, including 86 females and 96 males. Forty-eight breeds were represented, and age ranged from 6 months to 18 years (mean ± SD, 6.9 ± 3.3 years). Weights ranged from 1.5 to 65 kg (3.3 to 143 lb; mean ± SD, 20.2 ± 14.8 kg [44.4 ± 32.5 lb]). The initial injection of contrast medium was administered via cerebellomedullary injection in 100 dogs and via lumbar injection (L5-6) in 82 dogs, with a dose of iohexol ranging from 0.09 to 1.07 ml/kg (0.04 to 0.48 ml/lb; mean, 0.42 ± 0.10 ml/kg [0.19 ± 0.45 ml/lb]; iodine dose, 21.6 to 256.8 mg). Dose of contrast medium did not differ significantly between injection sites. Two injections were necessary in 59 dogs due to suboptimal image quality. Of these dogs, 12 (20.3%) received cerebellomedullary injections, and 47 (79.7%) received lumbar injections. The second dose of iohexol ranged from 0.07 to 1.15 ml/kg (0.03 to 0.52 ml/lb; mean, 0.43 ± 0.16 ml/kg [0.19 ± 0.07 ml/lb]). Only 2 dogs were administered contrast medium at the cerebellomedullary cistern for both the first and second injections. Twelve dogs required a third injection, all of which were administered at the L5-6 intervertebral space. The third dose of iohexol ranged from 0.16 to 0.88 ml/kg (0.07 to 0.40 ml/lb; mean, 0.36 ± 0.20 ml/kg [0.16 ± 0.10 ml/lb]). Total iohexol dose ranged from 0.09 to 2.02 ml/kg (0.04 to 0.92 ml/lb; mean, 0.58 ± 0.30 ml/kg [0.26 ± 0.13 ml/lb]). Total duration of anesthesia ranged from 65 to 445 minutes (mean, 216.4 ± 75.4 minutes). Duration of anesthesia from administration of contrast medium to recovery ranged from 30 to 370 minutes (mean, 150.1 ± 73.9 minutes).

Thirty-seven dogs had lesions at C1-C5, 1 at C4-C6, 5 at C5-C6, 20 at C6-T2, 1 at C6-T5, 98 at T3-L3, 1 at L3-L4, and 9 at L4-S3; 1 dog had diffuse cervical lesions, and 5 dogs had multifocal lesions. Four dogs had no detectable lesions. One hundred twenty-one dogs had intervertebral disc disease, 16 had other extradural compressive lesions, 8 had caudal cervical spondylomyelopathy, and 33 had intramedullary disease. One hundred five (57.7%) dogs had surgery immediately after the myelogram. Seventy-seven (42.3%) dogs were recovered from anesthesia following the myelogram without surgery.

Thirty-nine (21.4%) dogs had at least 1 generalized seizure following (within 1 hour of recovery) or during myelography. Significant differences were not detected in duration of anesthesia from injection of contrast media to recovery; iohexol dose, number of injections, breed, sex, or lesion type between dogs that did and did not have seizures. Weight was correlated with seizure risk; dogs that weighed >20 kg (44 lb; n = 79) had a significantly (P < 0.001) higher prevalence of seizures (34.17%, 27) than dogs that weighed < 20 kg (103), whose seizure incidence was 11.65% (12). Injection site was also significantly (P < 0.001) correlated with seizure activity. Of the 100 dogs that received a cerebellomedullary injection, 35 (35%) had a seizure, whereas only 4 (5%) of the 82 dogs that received lumbar punctures had a seizure. Dogs with cerebellomedullary punctures were 6.9 times as likely to have a seizure (95% confidence interval [CI], 2.2 to 21.2). Although dose per kilogram did not differ significantly between dogs that did and did not have a seizure, total volume of iohexol was a significant (P < 0.001) factor that influenced seizure risk. The mean total volume of contrast medium in dogs that did not have a seizure was 9.1 ml (SD, 7.1), whereas the mean in dogs that did have a seizure was 16.8 ml (SD, 8.0). Logistic regression analysis revealed that for each 5-ml increase in iohexol volume, the likelihood of seizure increased by 30% (95% CI, 8 to 67).

There was a significantly (P = 0.003) higher prevalence of seizures in dogs that did not have surgery immediately after myelography, compared with dogs that did have surgery. Of the 77 dogs that were recovered from anesthesia after myelography, 25 (32.5%) had a seizure, whereas seizures were observed in only 14 (13.3%) of the 105 dogs that had surgery after myelography. For dogs that did not have surgery, there was no major difference in duration of anesthesia between those that did and those that did not have a seizure. For those dogs that had surgery, those with seizures had significantly (P < 0.001) greater duration of anesthesia (by 1.4 hours), compared with those that did not have seizures.

There were a number of confounding issues to be
considered when identifying the risk factors for the development of seizures after myelography. Although volume, weight, surgical intervention and cerebellomedullary injections seemed to be significantly correlated with seizure risk, dogs that weighed > 20 kg were more likely (P < 0.001) to receive a cerebellomedullary injection, compared with dogs that weighed < 20 kg, which were more likely to receive a lumbar injection. Of the 100 dogs that received an initial cerebellomedullary injection, 62 (62%) weighed > 20 kg, whereas only 17 (20%) of the 82 dogs that received lumbar injections weighed > 20 kg. Likewise, although surgical intervention after myelography seemed to carry a reduced risk of seizures, there was a significant (P < 0.001) difference in weight among the surgical and nonsurgical groups. One hundred five dogs had surgery immediately after myelography, and of these, 80 (76.2%) weighed < 20 kg, whereas 25 (23.8%) weighed > 20 kg. Similarly, 69 (65%) of the dogs that underwent surgery also underwent lumbar myelography; whereas only 14 (18%) of the 77 dogs that did not undergo surgery received an initial lumbar injection. Most (81%) of the dogs that did not undergo surgery received iohexol via a cerebellomedullary injection. In a multivariate analysis, volume and cerebellomedullary punctures were independent factors contributing to an increased risk of seizure after myelography, whereas surgical intervention alone did not prove to be a predictor of seizure activity.

**Discussion**

In the study reported here, risk factors identified for development of seizures after myelography included weight > 20 kg and injection site; dogs that underwent cervical myelography had a significantly higher prevalence of seizures than those that underwent lumbar myelography. These findings are in general agreement with earlier research on metrizamide and iohexol in which weight and cerebellomedullary injections were positively correlated with risk of seizures. Our findings were not consistent with a previous report that implicated a breed and sex predilection in male Doberman Pinschers for developing seizures after administration of iohexol for myelography. It is likely that the increased prevalence of seizures in that group of dogs was a function of their large size and the fact that they were more likely to undergo cervical myelography. Lesion type, specifically caudal cervical spondylomyelopathy, has also been identified as a risk factor for seizures after myelography, compared with all other diagnoses, a finding our data did not support. In fact, there were no significant differences in prevalence of seizures among any of the dogs in our study with respect to location or nature of the lesion. Similarly, the percentage of Doberman Pinschers in our study that had a seizure did not differ significantly from the seizure prevalence of the other dogs in the > 20-kg group. Results of statistical analysis suggest that lesion type and breed alone do not predispose dogs to seizures after myelography but instead imply that dogs that are prone to developing caudal cervical spondylomyelopathy are more likely to be in the other high-risk categories (ie, large volume of contrast medium, cerebellomedullary injection, large breed) for this potential complication. Although receiving multiple cerebellomedullary injections was reported to be associated with an increased risk of seizures, only 2 dogs in our study were administered > 1 dose of contrast medium via the cerebellomedullary cistern. While 1 of these 2 dogs did have a seizure, we were not able to critically evaluate the importance of these findings because of inadequate sample size.

Contrary to our hypothesis, dose of contrast medium was not correlated with seizure activity. This was a surprising finding since numerous studies of metrizamide and iohexol suggest that total dose of contrast medium is related to the development of adverse neurologic effects. However, total volume did prove to be a significant contributing factor that influenced development of seizures; each 5-ml increase in volume increased the likelihood of seizure by 30%. Large injection volumes of metrizamide have been described as a variable associated with increased seizure risk, a finding not reported with iohexol. In a study of 107 dogs that underwent administration of metrizamide for myelography, injection volume > 7 ml had the most significant correlation with seizure risk, compared with all other risk factors.

One hypothesis for greater prevalence of seizures in large dogs, compared with smaller dogs, is that they receive larger total volumes of contrast medium, relative to the volume of the CSF; despite having the same dose per unit of body weight as smaller dogs. Perhaps it is incorrect to assume that the volume of the subarachnoid space increases in a linear fashion with respect to weight or that it varies substantially in dogs of different breeds and sizes. Determining dosage on the basis of body surface area rather than absolute weight has been proposed to reduce prevalence of seizures, but results of studies on metrizamide did not support this suggestion. To the author’s knowledge, this has not been evaluated with iohexol. Other parameters, such as crown-rump length, have also been suggested but have been found to be of limited value. Since an ideal means for estimating the appropriate dose of contrast medium has not been established, use of fluoroscopy during cervical myelography can be an aid in assessing the flow of the contrast medium in the vertebral canal and preventing untoward adverse effects caused by excessive contrast volume. Finally, the mean total dose (and therefore volume) of iohexol administered to dogs in our study was 0.38 ml/kg, which is greater than that recommended in the veterinary literature. In other veterinary institutions, adjustments in the amount of iohexol are often made on the basis of the animal’s size (ie, giving a smaller dose to large-breed dogs, relative to their weight). Investigation is warranted to determine whether the volume of contrast medium should be based on weight, surface area, length, or other reference points, and whether lower doses can be used without compromising the quality of the images.

Surgical intervention and prolonged duration of anesthesia after myelography, while reported for both iohexol and metrizamide to be protective against seizures, did not (independently) lower the prevalence of seizures in our study. Although a greater number of dogs that did not receive surgery had a seizure, compared with dogs that received surgery, results of multivariate analysis suggest that this resulted from the fact that significantly more of the dogs that did not receive surgery
weighed > 20 kg and received cerebellomedullary puncture. Additionally, there was no significant difference in total duration of anesthesia between dogs that received surgery and those that did not, implying that other risk factors may be responsible for the seizure activity. Of the dogs that did have surgery, there was a higher prevalence of seizures in those with prolonged duration of anesthesia. This was an unexpected result, since we predicted that dogs with extended anesthesia after myelography would have eliminated the contrast medium from the subarachnoid space prior to awakening, whereas those dogs that recovered from anesthesia immediately after myelography would still be subject to the neurotoxic effects of the iohexol. The clinical importance of this finding is unknown.

The neurotoxicity of intrathecally administered contrast medium is related to a number of properties, including its chemotoxicity and hyperosmolarity. Chemotoxicity is associated with the compound's lipophilicity (media with more lipid solubility have increased neurotoxicity) and its molecular structure, whereas hyperosmolarity promotes a neuronal ionic imbalance and allows a larger number of molecules to enter the CSF and extracellular fluid. The iodine atoms in iodinated contrast material are hydrophobic and are thought to be responsible for most of the direct effects on cell membranes. A nonionic contrast medium, such as iohexol, has large hydrophilic side chains that shield the iodine atoms to reduce neurotoxicity and is only slightly hyperosmolar at the concentration (240 mg of iodine/ml) used in our study. Iohexol also lacks the glucose side chain that is believed to be responsible for some of metrizamide's adverse effects. All of these properties suggest that iohexol should be less epileptogenic than metrizamide. Thus, it is unclear why the population of dogs in this study had a higher prevalence of seizures than expected.

Identifying risk factors for seizures in order to reduce prevalence of seizures was 1 of the fundamental goals of our study. Although larger dogs were more likely to receive contrast medium via a cerebellomedullary puncture, compared with small dogs, regression analysis revealed that injection site was an independent factor that influenced development of seizures. Our results suggest that it is preferential to perform myelography by administering iohexol via the L5-6 intervertebral space in order to minimize the risk of seizures. It has been proposed that optimal image quality is obtained when the contrast medium is injected in the site nearest the suspected spinal cord lesion. This is not necessarily in agreement with our experience at VHUP and that of other veterinary institutions, and we believe that sufficient opacification of the cervical spinal cord may be obtained via lumbar myelography. In a study of 300 human patients, 86.5% of cervical myelograms obtained by use of lumbar injection were deemed of adequate quality. Although cerebellomedullary injections are technically less demanding, lumbar injections should be attempted whenever possible, particularly when fluoroscopy is available, in an attempt to decrease prevalence of seizures. It has been reported that neurotoxicosis can be reduced if contrast medium is prevented from flowing rostrally into the basilar subarachnoid space and ventricular system. For animals in which lumbar injections are not possible, this can best be accomplished by maintaining the head in an elevated position and injecting contrast media slowly during cervical myelography. It is of interest that most seizures occurred within 1 hour of recovery. This suggests that vigilant patient monitoring is most essential in the immediate postanesthetic period and implies that anesthesia either obscures clinically apparent seizures or raises the seizure threshold.

References