[redacted]

[redacted]

[redacted]

Re: Conray contrast agent overdose

Dear Dr. [redacted],

Please find attached the write-up for Mr. [redacted] in regards to the conray contrast agent overdose. Please add this documentation to the final report. The time spent on this write-up totals fifteen hours as requested.

Brief Summary:

Mr. [redacted] was administered an overdose of Conray contrast product while undergoing a myelogram procedure for paroxysmal vertigo. The patient developed seizures, impairments in cognition and memory function, and disabling neuromuscular deficits. Given the contraindicated dose that Mr. [redacted] received and the direct entry of the agent into the CNS, it is probable that significant and irreversible contrast neurotoxicity – death of brain and spinal cord cells -occurred and caused damage to neural tissue contributing to each of the neurologic and neuromuscular deficits. Mr. [redacted] was neurologically intact before the contraindicated intrathecal injection (chemotoxicity). A reasonable, clinically valid, and scientifically sound explanation of his current neurological deficits is the acute neurotoxicity, from which he did not fully recover. My opinions are stated with reasonable pharmacological certainty.

Thank you,

Stephanie Tedford, PhD
Email: Setedford@gmail.com

Re: Conray contrast agent overdose

Materials Reviewed:

- Neuropsychological Evaluation January 2015
- Medical Center records
- United States Food and Drug Administration MedWatch reports for Neurotoxicity following Conray and other Iodinated non-ionic contrast media
- Prescribing information for Conray
- Defense expert witness disclosures
- Literature describing the toxicology and pharmacokinetics of Conray and other ionic/non-ionic contrast media effects on brain tissues, including the mechanisms of actions of the neurotoxicity. Citations to the literature are noted in the body of this report.

Re: Conray contrast agent overdose

CASE DISCUSSION AND SUMMARY OF THE LITERATURE REGARDING INTRATHECAL CONRAY CONTRAST MEDIA OVERDOSE, SEIZURES, COGNITIVE IMPAIRMENT, NEUROMUSCULAR AND OTHER TOXIC MANIFESTATIONS

There are several serious adverse events associated with the use of Conray [Iothalamate], and similar iodinated contrast agents, including a variety of neurologic manifestations. These effects can range from epileptic seizures and seizure-like activity, amnesia and cognitive disability to a myriad of neuromuscular deficits. Although these effects are rare, they are documented in the literature and are widely considered to be related to the toxicity of the contrast agent. The association of contrast agents and serious adverse events have been reported in a variety of procedures and by differing routes of administration leaving much evidence for their direct involvement.

CASE HISTORY:

[redacted] who presents with a history of persistent neurological and motor-related impairments following exposure to intrathecally administered Conray contrast product [Iothalamate]. Mr. [redacted] was inadvertently administered an intrathecal injection of Conray during a myelogram procedure on July 1, 2013. The procedure was conducted as part of a work-up for paroxysmal vertigo which may have been related to a left Meckel's Cave cyst previously identified by MRI. Following injection, Mr. [redacted] immediately exhibited signs of contrast-induced neurotoxicity including lower limb disturbances, seizure activity, cognitive dysfunction and memory loss. He also presented with peripheral paresthesis, bilateral lower extremity tingling and spasms. It was quickly determined that he had been administered the incorrect contrast product for intrathecal use in myelography; Conray contrast media is never to be administered intrathecally and contraindicated for use in myelography. A CSF lavage with 100 cc of saline, in addition to a lumbar drain, was initiated to remove the contrast product from circulation. Mr. [redacted] was also treated transiently with Keppra to control his seizure activity. Mr. [redacted] was released four days following the procedure. Following discharge, he reports persistent cognitive impairment including the inability to concentrate, multitask and dull tension-like

headaches. He also exhibits neuromuscular impairments such as diffuse hyperreflexia, dizziness, unsteadiness, association of generalized weakness and intermittent muscle spasms.

In May 2014 (10 months' post-procedure), Mr. [redacted] met with Dr. [redacted] discussed his continuing problems with fatigue, spasms in his legs and a buzzing sensation in the lower extremities that generally presented following several days of work. He also complained of fluctuating blurred vision. Upon examination, Dr. [redacted] described slightly increased muscle tone, evidence of a fine mild past postural tremor and extreme sensitivity to flashing lights. She reported the following diagnoses: "1) recent episode of accidental exposure to Conray Ionic Contrast Agent during myelogram-rapid resolution of symptoms, treated with CSF lavage, lumbar CSF drain and drug induced sedation; 2) improving, mildly persistent gradual symptoms: mild irritability/spasms, fatigue, vibratory paresthesis, tremor, blurriness of vision; 3) history of paroxysmal vertigo questionably caused by Meckel's arachnoid cyst-no recurrent symptoms."

In May 2014, Mr. [redacted] also met with neurologist Dr. [redacted] for motor complaints; his chief complaint being tremor. Motorically, Mr. [redacted] demonstrated grossly reduced dexterity in both left and right hands and changes in reflex activity. Cognitively, Dr. [redacted] noted Mr. [redacted] "unusually persistent loss of mental endurance including abilities of concentration, problem solving, attention, attending to tasks involving complexity, and aspects of communication." He states that "these features are fully plausible as a residuum of his injury due to the fact that (a) prior similar cases resulted in patient death (b) his early convalescence was marked by much greater loss of neurological function, with global disruptions of cerebral function including with cognition and coordination".

Most recently, Mr. [redacted] underwent a neuropsychological evaluation conducted by Dr. [redacted] in November/December of 2014. Mr. [redacted] described a number of physical symptoms and noted in particular, that vibratory sensations are severely stressful. The self-described "electrical buzzing" is a constant and Mr. [redacted] states " I am vibrating all of the time and I get the chills." He describes the vibrations acutely in his legs but notes that it will involve the whole body and that his head feels hollow. He experiences headaches and describes feeling that his "brain is bouncing." Headache pain is localized throughout. Mr. [redacted] also complained

of variable levels of fatigue and disruptions in balance resulting in recurrent falls. His visual disturbances have improved following ophthalmologic intervention. He reports a diagnosis of "a disconnect between my eyes and my brain" by his eye specialist and is undergoing vision therapy. The patient also reports the development of joint pain since his contrast dye exposure. Cognitively, Mr. [redacted] describes many deficits in executive functioning. He reports problems with his attention span, future planning skills, working memory and his multitasking capabilities.

During the neuropsychological evaluation, Mr. [redacted] exhibited significant signs of anxiety that were apparent throughout the diagnostic interview and a portion of the psychometric testing. Mr. [redacted] displayed impaired performance on problem-solving and executive functioning assessments. Specifically, he presents with poor organizational and planning skills. His neurocognitive testing showed signs of cognitive dysfunction, or decline, and he displayed difficulty with visual-spatial tasks. He also showed varying issues with cognitive flexibility. Memory testing demonstrated mild difficulty with visual memory. The motor examination revealed reduced fine motor coordination, motor speed and dexterity. His psychological assessment was consistent with an underlying somatic symptom disorder of moderate severity. Underlying neurological deficits are not precluded with this diagnosis. It is only noted that these psychological contributors may exacerbate the concomitant disabilities.

Prior to Mr. [redacted] unintentional exposure to Conray, he was a neurologically sound individual whose primary complaint was for symptoms of vertigo, which he mentioned had largely subsided by the time he underwent the myelography procedure. Drs. [redacted] and [redacted] indicate that Mr. [redacted]s inadvertent toxic exposure most likely contributes to his persistent display of symptoms. They report no further understanding of long-term sequelae following such an incident as there is relatively no information available on residual effects. The majority of literature reports acute findings in such cases and an unfortunate number of patients that receive inadvertent intrathecal injections of contrast product result in death.

MANUFACTURERS NOTES [CONRAY, IOTHALAMATE]

The first-generation contrast agents available for imaging use were ionic, water-soluble products that were extremely neurotoxic and deemed unsuitable for procedures such as myelography.

Re: Conray contrast agent overdose

Direct application of these products in the central nervous system (CNS) resulted in severe toxicity and mortality. Intrathecal administration of these products was therefore not employed. Adverse reactions following ionic contrast agents are higher in incidence (3.8-12.7%) than with nonionic contrast agents (0.6-3.1%) (Christiansen, Toxicology, 2005). Pharmacological improvements and the development of newer nonionic compounds have made intrathecal administration for myelography a possibility. Older ionic compounds, like Conray contrast dye are still employed however their use is limited and does not include intrathecal administration.

Conray contrast dye is an ionic, aqueous product intended for use as a diagnostic radiopaque medium. The Conray product that was administered to the patient, Mr. [redacted], was Conray-60 which contains 60% w/v iothalamate meglumine, which is 1-deoxy-1-(methylamino)-D-glucitol 5-acetamido-2,4,6 triiodo-N-methylisophthalamate (salt formulation). Each ml of the solution contains 600 mg of iothalamate meglumine, 0.09 mg edetate calcium disodium and 0.125 mg of monobasic sodium phosphate. Conray-60 provides 282 mg/mL organically bound iodine and is a hypertonic solution with an osmolarity of 1000 mOsmol per liter (1400 mOsmol per kilogram). Iothalamate rapidly enters blood circulation and is excreted by the kidneys unchanged in urine through glomerular filtration. Optimal contrast enhancement typically is observed after peak blood iodine levels are reached and is suggested to represent the accumulation of iodine. Following intravascular administration of Conray, the observed alpha and beta half-lives are typically 10 and 90 minutes, respectively.

Due to the ionic properties and relative toxicity of iothalamate, intrathecal use and direct application to the CNS is not recommended. Serious adverse events can occur if iothalamate is inadvertently administered intrathecally and the manufacturers' list the following intrathecal reactions: "death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema." Reports of serious neurologic sequelae (e.g., permanent paralysis) are also noted following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord using Conray. Additional neurological reactions reported by the manufacturers include "spasm, convulsions, aphasia, paresis, paralysis resulting from spinal cord injury and pathology associated with syndrome of transverse myelitis, visual field losses which are usually transient but may be permanent, coma and death." Miscellaneous effects include "headache, trembling,

shaking, chills without fever and lightheadedness. Temporary renal shutdown or other nephropathy." Additional signs of CNS disturbances from contrast products include reports of mild and transitory perceptual aberrations (e.g., depersonalization, anxiety, depression, hyperesthesia, disturbances in speech, sight, or hearing, and disorientation, hyperreflexia or areflexia, hypertonia or flaccidity, restlessness, tremor, echoacousia, echolalia, asterixis or dysphasia), profound mental disturbances (various forms and degrees of aphasia, mental confusion or disorientation), transitory hearing loss or other auditory symptoms and visual disturbances (believed subjective or delusional), persistent cortical loss of vision in association with convulsions and ventricular block.

There are over 4000 adverse events listed in the MedWatch Adverse Event Reporting Database for adverse reactions to contrast agents. The most frequently reported adverse reactions associated with all contrast products that may be related to neuromuscular damage include dizziness (309), convulsion (220), hypoesthesia (207), tremor (200), convulsion NOS (149), paresthesia (140), hypoesthesia oral (82), paresthesia oral (80), muscle spasms (76), rigors (66), hemiparesis (55), grand mal convulsion (53), Tremor NEC (49), and paresthesia NEC (45). More specifically, reports of adverse events associated with Conray include tremor NEC (11), dizziness (EXC vertigo, 9), muscle spasm (8), convulsions NOS (5), tremor (3), paresthesia (3), rigors (2), muscle contractions (2) and single reports of hypoesthesia oral, paresthesia NEC, muscular weakness, musculoskeletal stiffness, gait disturbance, muscle rigidity, myoclonic jerks, muscle cramp and tonic clonic movements. Adverse events reported for intrathecally administered Conray include muscle spasms (5), hypoesthesia (3), paresthesia (2), muscle contracting involuntary (2) and single reports of tremor, confusional state, muscular weakness, musculoskeletal stiffness, gait disturbance, muscle rigidity, myoclonic jerks, mental impairment, impulsive behavior and personality change.

The remainder of this report examines the neurobiology of seizures, cognitive function, memory and neuromuscular deficits, and superimposes the toxicological findings and mechanisms of contrast media and other neurotoxic drugs on the neurobiology, attempting to provide a rational explanation why a patient like, Mr. [redacted], who was neurologically intact before the intrathecal Conray toxic exposure is now neurologically deficient and neurologically disabled.

Re: Conray contrast agent overdose

CONTRAST MEDIA NEUROTOXICITY

CONRAY [IOTHALAMATE]: MECHANISMS FOR NEUROTOXIC INJURY

The exact mechanisms underlying cerebral insult following contrast agent administration remains uncertain. Several mechanisms of cellular neurotoxicity on selected regions of the central nervous system (CNS) affecting sensory, motor, cognition and memory function are described. When given systemically, entry of the contrast agent into the brain parenchyma is attributed to breakdown of the blood brain barrier (BBB). BBB disruption can be explained by the hyperosmolarity, lipid solubility and chemotoxicity of iodinated contrast agents (Uchiyama, AJNR Am J Neuroradiol, 2004). Experimentally, the BBB will open upon exposure to hypertonic solutions in the bloodstream or in contact with the surface of the brain (Rapoport, Science, 1971). Conray has significantly higher osmolarity (1400 mosm/kg) when compared with that of plasma (285 mosm/kg), blood (300 mosm/kg) and CSF (301 mosm/kg), which may contribute to increased permeability of the BBB. The hypertonic contrast solution attracts water out of the endothelial cells of brain vessels causing cellular dehydration, shrinkage and subsequent separation in tight junctions and enhanced endothelial pinocytosis, thereby allowing for entry of the contrast agent. Lipid solubility, or the octanol/water partition coefficient of the contrast medium anion, regulates the drugs ability to pass through membranes of the endothelial cells that comprise the BBB and is directly correlated with their ability to induce toxic effects. Similar mechanisms likely contribute to breakdown of the blood-CSF-barrier (BCSFB) allowing access to the spinal cord. Iothalamate has high lipid solubility and is ranked number 1 for neurotoxicity out of a comparison of eight contrast products (Rapoport et al., Am J Roentgenol Radium Ther Nucl Med., 1974). The severity of the barrier dysfunction is subject to the relative chemotoxic action of the contrast agent. Upon entry of the contrast medium into the subarachnoid space, it transcends the extracellular space by passive diffusion through the pia mater. Exposure of high doses of iodine to neural tissue can induce severe disruption in cellular functions including changes in neural transmission and cell death. The central chemical structure of a contrast molecule is the benzene ring and benzoic acid derivatives affect cellular membrane permeability and electrical activity of neurons with a potency that is highly correlated with their lipid solubility (Rapoport et al., Am J Roentgenol Radium Ther Nucl Med., 1974). BBB breakdown following ischemic stroke allows entry of contrast agent into intracranial

compartments of the brain, where it alters neural activity (Bryan, Radiology, 1982). Altered neuronal membrane permeability and depolarization properties of neurons may contribute to dysfunctional neural communication. Changes in neurological activity, e.g., the development of seizures, neuromuscular and cognitive deficits, occurs when nonionic contrast products penetrate extracellular and intracellular regions of the CNS. Entry of the contrast agent into the brain or spinal cord can result in profound neurotoxicity and serious complications.

There is some level of inherent risk with intrathecal drug administration as this route places the drug in direct and immediate contact with the CNS. Conray contrast product has not been formulated for intrathecal use; the ionic properties, significant hypertonicity and relative chemotoxicity of the drug makes it a dangerous compound for direct CNS application and therefore, it is contraindicated for this use. During the lumbar intrathecal administration of Conray contrast agent, the drug is injected into the subarachnoid space of the spinal column directly mixing the product with CSF. CSF is secreted at the choroid plexus and occupies spinal and cranial subarachnoid spaces where it has direct contact with the brain and spinal cord. The choroid plexus epithelium composes the BCSFB, and this barrier displays fundamentally different properties than the brain microvascular endothelium, which forms the BBB. CT scans show that contrast agents circulate freely throughout the subarachnoid space in a consistent manner similar to CSF flow. The contrast medium infiltrates the cerebrum and cerebellum from adjacent subarachnoid spaces. Studies with ^{131} I-labeled metrizamide (nonionic contrast agent) demonstrate the penetrance of the drug into the brain when delivered intrathecally. The development of adverse reactions is most prominent during the periods of maximum brain penetrance (Drayer and Rosenbaum, Acta Radiologica. Supplementum, 1977).

CONTRAST-MEDIATED ADVERSE EVENTS

Contrast-induced adverse reactions are categorized as chemotoxic or idiosyncratic reactions. Chemotoxic reactions are related to the physiochemical properties of the contrast medium and dosing parameters. Pharmacodynamic properties of the contrast agent on tissue are included in this category. Idiosyncratic reactions are unpredictable adverse drug reactions that do not manifest in most patients. There are many published reports that detail contrast agent-mediated complications. The brain is a homeostatic organ and changes in osmolarity due to the

hypertonicity of the contrast product may not only disrupt the BBB and BCSFB, but in severe instances may cause widespread osmotic changes in the CNS sufficient to induce global cell death. One case reports fatal brain edema in a patient who experienced contrast agent overdose following aortography. Generalized seizures began after the contrast agent was injected and a CT scan performed 22 hours' post-injection showed the contrast agent in the arteries at the basal brain. CT also revealed increased density in the cerebral cortex, basal ganglia and thalamus consistent with the existing intracerebral agent. The patient succumbed to the cerebral insult and 48 hours post contrast injection, a CT confirmed high concentrations of the contrast agent still present in the patient. In addition, 4 hours' post-mortem, an iodine assay by fluorescence excitation revealed extremely high iodine concentrations throughout the brain (See table below). The concentrations observed in the cortical, thalamic and hippocampal regions were elevated and there is no question that exposure to these levels of iodine would completely disrupt cellular function. An autopsy reported diffuse edema within the cerebrum and the cerebellum and subarachnoid hemorrhage. The authors report that the doses administered to this patient were grossly excessive and greatly exceeded the maximum recommended dose (Junck & Marshall, AJNR, 1986). Similarly, another patient who underwent aortography developed seizures, cortical blindness and renal failure following contrast agent administration within a recommended dosing protocol. A follow up CT revealed high iodine concentrations in the cortex and mild brain edema (Studdard, J Neurosurg, 1981). This report demonstrates the potential of serious contrast-induced disturbances even within a normal dosing protocol.

Brain Region	Iodine Concentration (mg/g)	Estimated concentration compared to normal *
Frontal cortex	1.01	50,000x
Thalamus	1.4	70,000x
Hippocampus	1.01	20,000x

**Iodine concentration in a control brain sample was 0.00002 mg/g. [data taken from Junck & Marshall, AJNR, 1986]*

Re: Conray contrast agent overdose

There are few published reports on the inadvertent administration of intrathecal contrast agents. Three reviews of varying detail suggest a mortality rate of 27%-43% of patients delivered intrathecal ionic contrast agents (Leede et al., Eur Radiol, 2002) (Rosati et al., Eur J Radiol, 1992)(Roux and deschamps, Vet Radiol and Ultrasound, 2007). The onset of neurotoxic symptoms following intrathecal injection is typically immediate. Clinical manifestations can be described as the abrupt presentation of severe leg pain followed by myotonic than clonic spasms of the lower limbs and finally the full trunk of the body. Myoclonus and jerky movements tend to increase in duration, intensity, and location as the drug accumulates. Ascending Tonic-clonic seizure syndrome is often used to describe these symptoms as they begin in the legs following lumbar injection and ascend upwards through the CNS. In one review, 11/32 cases were fatal and these subjects all presented with severe seizures and subsequent hyperthermia, metabolic acidosis and rhabdomyolysis (dissolution of skeletal muscle). While outcomes of these patients were categorized by mortality (i.e., survived or death), three surviving patients were noted as having residual deficits including motor weakness and headache (Leede et al., Eur Radiol, 2002). Another case study describes the inadvertent intrathecal administration of ionic contrast product ioxitalamate resulting in severe neurotoxicity. A CT scan conducted seven hours' post-injection revealed increased density in all intracranial CSF spaces, including basal cisterns, cortical sulci and ventricles. Lumbar CSF draining and saline replacement aided in clearing the contrast from the patient's system and a CT scan performed at 72 hours revealed no residual contrast product. When administered intrathecally, the median lethal dose of ionic contrast agents is lowered, greatly reducing their safety margin. The initial studies of intrathecal Conray use revealed unsatisfactory safety margins and association with the development of adhesive arachnoiditis; an effect attributed to the osmolality of the contrast solution (Rosati et al., Eur J Radiol, 1992).

Overall, significant changes in the osmolarity may contribute to leakage of a contrast product across the BBB and BCSFB into the CNS. In addition, profound changes can induce considerable brain edema which may be detrimental to brain function. In Mr. [redacted] case, the barriers were bypassed by an intended direct intrathecal injection. This inadvertent administration caused the CNS to be showered with neurotoxic, chemotoxic, hyperosmolar chemicals – poisonous to neural tissue. Mr. [redacted] displayed immediate signs of neurotoxicity, consistent with symptoms reported in the literature (i.e., leg disturbances followed by seizures).

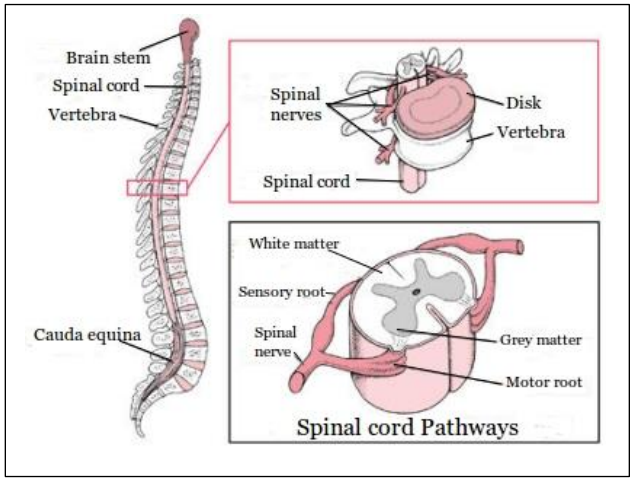
Re: Conray contrast agent overdose

CONTRAST-INDUCED NEUROMUSCULAR IMPAIRMENT

The toxic effects of ionic contrast exposure may contribute to the development of sensory/motor-related impairments exhibited by the patient. Mr. [redacted] describes or has been diagnosed with symptoms consisting of persistent vibratory paresthesias, fine mild postural tremor, hyperreflexia, increased muscle tone, bilateral lower extremity tingling and spasms, reduced fine motor coordination, motor speed and dexterity. This myriad of sensory/motor deficits has persisted since the contrast exposure suggesting permanent damage to relevant structures in the nervous system.

It is well known that intrathecal injections with toxic substances can severely damage components of the spinal cord leading to motor and sensory disturbances and even death. Simply, the composition of the spinal cord includes motor and sensory contributions, and white matter fiber tracts that carry information to and from the brain. Nerve fibers entering the dorsal root relay sensory information whereas fibers leaving the ventral root of the cord carry motor information to the muscles. Damage to the dorsal or ventral roots result in sensory or motor loss, respectively. Toxic neuropathy is used to describe nerve injury subsequent to a drug exposure. Typically, patients present with distal axonopathy after toxic drug exposure, or a dying-back type of degeneration of the nerve fiber. Sensory, motor and autonomic nerves may be damaged and common clinical symptoms overlap with those exhibited by Mr. [redacted] (e.g., tingling and numbness, muscle weakness, dizziness, vibratory paresthesia). Over forty drugs have been identified with neuropathy as a potential complication.

Re: Conray contrast agent overdose



In 2007, intrathecal administration of methotrexate and cytarabine were associated with widespread reports of paraplegia and paraparesis. It was determined that these drugs were contaminated with traces of vincristine, a chemotherapeutic drug that is neurotoxic when directly applied in the CNS. It is commonly known that certain chemotherapeutics have the potential to induce spinal nerve damage resulting in neuromuscular problems. The majority of systemic chemotherapeutic drugs poorly penetrate through the BBB, but readily pass through the BCSFB, which provides rationale for the preferential toxicity of the sensory neurons of the dorsal root ganglia in patients receiving chemotherapy. Previous records of intrathecal vincristine administration show severe spinal nerve damage (ascending rediculomyopathy) and fatalities. Surviving patients are reported to have residual motor weakness and paraplegia. For patients delivered the contaminated intrathecal methotrexate/cytarabine, the outcome was diagnosed as toxic axonal neuropathy. Ninety-one cases were characterized and of these cases patients exhibited motor weakness (100%) and difficulty rising from squatting position (100%), reduced muscle power (59%, proximal less than distal; 21%, proximal equals distal, both are minimal; 20%,proximal and distal-none), sensory abnormalities (36%, hyperalgesia; 74%, bilateral sensory loss from T10 below; 18%, loss of sensation in saddle area) and abnormal reflexes (90%, ankle and knee jerk reduced/absent; 80%, abdominal reflex reduced/absent; 64%, anal reflex absent; 26%, Bilateral Babinski's signs). In addition, 83% of patients showed reduced slow nerve conduction in lower extremities by EMG (Zeng et al., J Clin Oncology, 2011).

There are case reports that provide pathological evidence for the devastating effects of drug-induced toxic insult to the spinal cord resulting in severe neuromuscular damage. Methylene blue, a commonly employed dye among other indications, is highly toxic to the nervous system when delivered by intrathecal injection. One case report describes a patient who presented with paraparesis within 24 hrs of the intrathecal methylene blue injection. Improvement was noted in the strength of the lower limbs in subsequent months followed by an unfortunate increase in the

progression of the paraparesis. Four months after the toxic insult the patient developed sensory loss and a clinical diagnosis of complete loss of power in the right lower limb was obtained at 18 months after the exposure. Three years post-injection the patient was diagnosed with total paraplegia with a level at T9 that persisted until the patient's death five years later. Post-mortem examination of the spinal cord exposed fibrous thickening of the dura and arachnoid membranes located on the lower thoracic and lumbar spinal cord. There was extensive loss of myelinated fibers located in the cauda equine and nerve roots had intertwined together to form a fibrous mass. The spinal cord itself had grossly shrunk and softened with cystic changes particularly noticeable in the lumbar segments. The extent of damage was most significant in the lumbar region (presumably near injection site). The dorsal aspects of the spinal cord at the L5 segment were mostly deteriorated with remains of some anterior horn neurons still present in the grey matter in addition to short inter-segmental tracts of white matter. Extensive fibrosis and thickening of the meninges were observed. The most severely affected segment was the first lumbar region where cord shrinkage and near complete deterioration of myelinated tracts and cell bodies were observed. The mechanisms underlying methylene blue toxicity are unclear but it is suggested that the chemotoxicity of the compound itself and the low pH (pH 3.6-3.7) of the solution likely contribute to these effects. The authors describe three phases of spinal cord and nerve root insult following the intrathecal injection in this patient. The initial phase consisting of direct damage to the surface of the cord and exposed blood vessels resulting in probable inflammatory and vasculature changes. The second phase encompassed the transient improvement in limb power that may be related to regression of edema around areas of infarction in the cord. The final phase consists of the advancing paraplegia, presumably caused by progressive ischemia of the spinal cord with associated fibrosis and scarring of the meninges. Evidence of blood vessel damage was discovered at the post-mortem examination, and this likely contributed to infarction of the cord and nerve roots. Overall, the pathological evidence discussed following this drug-induced toxic event provides support for significant damage following an acute exposure of a toxic product to the CNS, specifically in regards to spinal cord and nerve root insult leading to prominent disability. The sensory/motor symptoms expressed by Mr. [redacted] are likely due to similar toxic damage that followed the intrathecal exposure of Conray to the spinal cord resulting in nerve root damage.

Re: Conray contrast agent overdose

Chronic alcohol consumption is associated with the development of peripheral neuropathy. Alcoholic neuropathy arises from substantial long-term drinking which directly impairs nerves fibers in the spinal cord. Following ingestion of alcohol, systemic circulation puts ethanol in contact with the BBB and BCSFB where it actively diffuses into the CNS. The mechanisms behind alcoholic neuropathy are unclear, but direct ethanol toxicity on spinal cord cells has been suggested. Clinical reports observe a dose-dependent relationship between severity of neuropathy and total life-time exposure to ethanol. The generation of reactive oxygen species leading to free radical damage to nerves and nutritional deficits have also been proposed. The pathological underpinnings are likely multifaceted and occur by combination of direct ethanol toxicity and toxic effects by its metabolites and by products and nutritional deficiencies. Clinical symptoms are slow in onset and include abnormalities in sensory, motor, autonomic and gait functions. The development of painful sensations in extremities is the hallmark feature of alcoholic neuropathy. Motor weakness and sensory/motor deficits typically extend proximally into the limbs as the disease progresses. Pathological evidence suggests axonal neuropathy with reductions in nerve fiber densities (Chopra and Tiwari, Br J Clin Pharmacol, 2011).

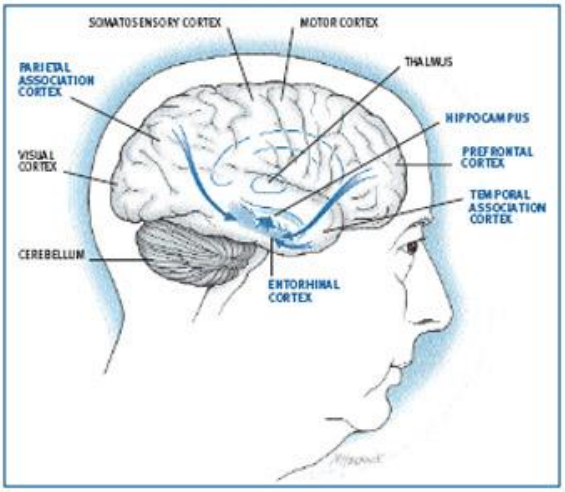
There are limited studies that have investigated the effects of contrast agent exposure on spinal cord physiology. In one report, the effects of ionic and nonionic contrast agents were studied on segmental reflexes in the spinal cords of cats. Lumbar segments of the cord were exposed to each agent. In general, exposure of hypertonic agents produced a transient decrease in all reflex activity (flexor monosynaptic reflex, extensor monosynaptic reflex and polysynaptic flexion reflexes). Isotonic solutions did not significantly affect monosynaptic responses, but increased the amplitude of polysynaptic responses, and altered the flexion reflex on the extensory monosynaptic reflex from inhibitory to excitatory. Isotonic solutions increased spontaneous ventral root activity (Bryan et al., Invest Radiol, 1981). Contrast agent methylglucamine diatrizoate increases segmental spinal polysynaptic reflexes and also electrically-induced cortico-spinal responses. Of note, iothalamate increases the amplitude of segmental spinal polysynaptic reflexes (Hilal et al., Radiol, 1977). Altogether, these preclinical studies indicate a direct effect of contrast agents on the spinal cord.

Re: Conray contrast agent overdose

CONTRAST-INDUCED SEIZURES AND COGNITIVE DEFICITS INCLUDING MEMORY LOSS

Immediately following the intrathecal injection of Conray, Mr. [redacted] developed prolonged seizure activity along with acute deficits in cognition and memory function. Mr. [redacted] does not report any ongoing issues with seizure activity although he is severely sensitive to flashing light. He reports continued problems with his attention span, future planning skills, working memory and his multitasking capabilities. His 2015 neuropsychological evaluation noted that he showed varying issues with cognitive flexibility and signs of cognitive decline, such as reduced ability with visual-spatial tasks. His memory testing demonstrated mild difficulty with visual memory. A review of the MedWatch reporting database lists 676 cases of adverse reactions related to cognitive impairment, seizures and amnesia with nonionic radiographic contrast agents. The neurological underpinnings related to contrast-induced seizures, cognitive and memory dysfunction are discussed below.

There is substantial evidence from both preclinical and clinical reports for the development of seizures following administration of iodinated contrast agents. Although epileptic seizures are a rare occurrence (typically observed in <1%), they are a well-documented complication with reports dating back to the 1980's. While rare, the development of seizure activity is a serious adverse event and patients with a history of epilepsy are restricted from the use of contrast agents. Epileptic seizures generally occur within 10 hours following injection of the contrast product and are self-limited. It is widely accepted that injection of the contrast product is directly related to the appearance of seizures or seizure-like activity. Compelling clinical evidence from CT reports following contrast-induced seizures show high levels of remaining contrast in the brain and enhancement in cortical brain regions (Numaguchi, J Comp Assisted Tomography, 1984). Preclinical studies report that administration of contrast agents are epileptogenic when directly exposed to brain tissue in rabbits (Rapoport, Acta Radiol, 1974) and in rats (Giang and Kido, Radiology, 1982). Contrast agent Iopamidol slows electroencephalographic (EEG) activity, increases the appearance of slow brain waves and seizures, and induces a shift in energy towards slower brain frequencies (0.5-3.5Hz) (Caille, AJNR, 1983). While the precise mechanisms underlying seizure induction are not known, it is suggested that contrast-mediated changes in neural activity within subcortical circuits induce seizures at the thalamic level and



disruptions in thalamocortical communication (Caille, AJNR, 1983). The neural circuits involved in seizures are acutely and may be permanently altered structurally and functionally following a seizure episode. These changes can underlie subsequent cognitive impairment commonly witnessed in epileptic patients. Acute presentation of altered cognitive abilities and memory loss can develop following seizures.

In the CNS, long term potentiation (LTP) and depression (LTD) are two cellular events believed to underlie neuroplasticity, the functional readout for learning and memory processes. Disruptions in LTP are observed following pharmacologically-induced seizures. For example, animals with 10 flurothyl-induced seizures demonstrate reduced hippocampal LTP and behavioral deficits in spatial learning and memory tasks (Zhou JL et al., Eur J Neurosci, 2007). Mice treated with repeated systemic administration of SKF81297 to induce kindled seizures display hyperactivation of the mTOR signaling pathway in the hippocampus, disrupted LTP in the dentate gyrus and altered recognition memories (Gangarossa, Hippocampus, 2014). Electrically-induced convulsive seizures disrupt spatial learning and also reduce LTP processes in the hippocampus (Reid & Stewart, Seizure, 1997). In humans, reductions in LTP are observed in epileptic focal regions located in the hippocampus (Beck, J Neurosci, 2000). The accumulated evidence suggests that seizures can impact on neural substrates within critical cortical and subcortical structures to induce cognitive and memory disturbances. Acute and permanent presentation of altered cognitive abilities and memory loss can develop following seizures, however, given the contraindicated dosing and toxic exposure, it is likely that persistent deficits exhibited by Mr. [redacted] are due to damaged neurological substrates induced by the contrast agent.

The brain's mesial temporal structures are critically involved in the epileptogenic network but are also recognized as key structures involved in memory function. The process by which specific aspects of an event are encoded and stored in the brain continue to be elucidated. These processes include memory formation, storage, retrieval, and modification. The internal representation of an object consists of a diffuse network of cortical neurons that are activated by

the external stimuli. The variety of learned information and subsequent memory may not all be processed and stored by the same neural hardware in the brain. Thus, there is no single region of the brain that can be identified as the location for these events. Neural plastic changes in the brain are marked at the cellular level as a putative locale for memory. Changes in neuroplasticity occur throughout the CNS and therefore, it is generally accepted that memory storage occurs diffusely within the brain and even the periphery, may be dependent on the type of memory and may coincide with the experience associated with the information. Furthermore, the context in which a memory is initially stored may be modified over time.

Cognitive deficits, such as global amnesia, described as the "abrupt onset of disorientation due to loss of immediate and recent memory, retention of alertness and responsiveness, and ability to perform fairly complicated menta tasks" has been described in patients treated with iodinated contrast agents (Fisher, Acta Neurol Scad, 1964) (Giang, Radiology, 1989). Reports of amnesia associated with contrast agents' dates back to the 1950's (Hague, Acta Radiol, 1954). These effects can be permanent or transient and typically appear in onset within hours of contrast agent injection. The US FDA MedWatch reporting database lists 98 reports of memory dysfunction including amnesia, global amnesia, and memory impairment associated with the use of nonionic radiographic contrast agents.

Damage to the brain's mesial temporal lobe structures are a recognized substrate for permanent amnesia (Helmstädter and Elger, Brain, 2009). Adults with a diagnosis of temporal lobe epilepsy display deficits in memory function (Bell et al. Nature Reviews Neurology, 2011). Indeed, episodic memory dysfunction is considered a significant feature of temporal lobe epilepsy. During temporal lobe seizures, abnormal neural excitation in the hippocampus indirectly reduces excitation of neocortical structures. Of note, the lowest seizure thresholds within the brain are located in the hippocampus underscoring the relevance of this brain structure in seizure and memory dysfunction. Abnormalities in hippocampal function have long been studied and documented for their relevance in memory. Experimentally, permanent global amnesia is reported following bilateral lesions to the hippocampus (Arnetoli, Riv Patol Nerv Ment, 1983). More specifically, CA1 neurons located within the hippocampus are critical for retrieval of both short and long term memory (Izquierdo, Behav Brain Res, 2000). Contrast agents induce

excitatory changes in neurons and dose-dependent obliteration of recorded electrical activity in rat hippocampal slices (Giang and Kido, Radiology, 1982).

Additional cognitive effects include various forms of mental symptoms like difficulty planning, deficits in organizational skills, reduced motivational drives and depression. One study subjected patients to psychopathometric testing following myelogram procedures with contrast agents metrizamide and iopamidol. Mild mental deficits were observed following metrizamide and cognitive severity was dependent on the quantity of contrast medium diffusion into the intracranial space suggesting dose-related neurotoxicity (Galle et al., Neuroradiol, 1984). Contrast-related effects targeted to the frontal lobe are a plausible explanation for cognitive impairments. The frontal lobes are critical for executive functioning, also known as cognitive control. Altogether, altered patterns of hippocampal–neocortical interactions are suggested to underlie memory and other cognitive deficits. Englot and Blumenfeld's theory states that focal seizures spread to the thalamus, disrupting corticothalamic interactions. Thus, neurotoxicity in the frontal and temporal lobe structures, e.g., hippocampus, following contrast agent injection likely contributes to altered cognition and memory function.

Alternately, it has been proposed that amnesia and cognitive deficits following injection of contrast agents may be related to subsequent ischemia in bilateral limbic structures. Cerebral ischemia, or loss of blood flow and oxygenation in the brain, can lead to significant cell damage and death. There is preclinical evidence that cerebral ischemia disturbs object recognition in nonhuman primates and rats, a process commonly associated with medial temporal brain structures (i.e., hippocampus). Hippocampal neurons are at higher risk for degeneration following ischemia however neuronal degeneration is also observed in the entorhinal cortex and perirhinal cortex, medial dorsal thalamic nucleus, and cingulate cortex (Bachevalier and Meunier, Hippocampus, 1996). Ischemia-induced damage to neural structures may contribute to the symptoms exhibited by Mr. [redacted]. Cerebral ischemia also influences the integrity of the BBB. As discussed in previous sections, barrier breakdown contributes to contrast leakage into the CNS and subsequent neurotoxicity.

Re: Conray contrast agent overdose

CONTRAST-INDUCED VISUAL AND AUDITORY IMPAIRMENT: FURTHER EVIDENCE FOR CEREBRAL INSULT TO CORTICAL BRAIN STRUCTURES

Visual Impairment

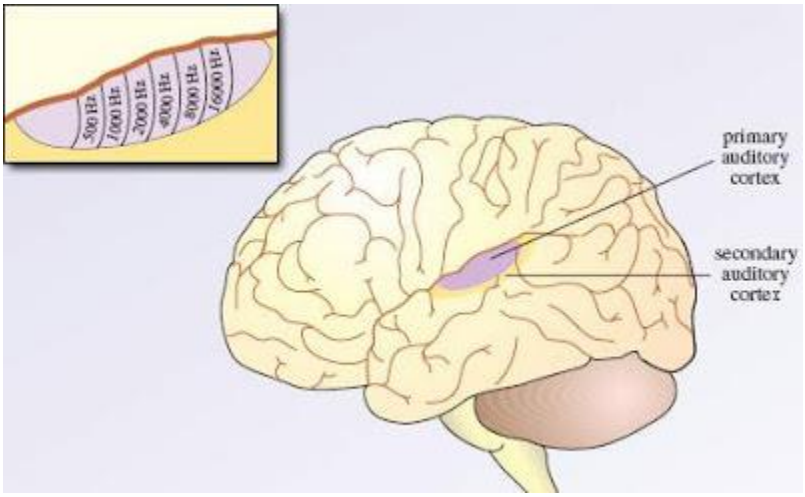
Following Conray exposure, Mr. [redacted] has complained of persistent fluctuating visual problems. Cortical blindness refers to visual impairment or total visual loss caused by bilateral destruction of the visual cortex (occipital cortex). Cortical blindness is a rare, but well-documented complication of contrast agent administration and can be transient or permanent. The MedWatch database reports a minimum of 66 adverse events associated with ocular disturbances including reductions in visual acuity and blindness following injection of contrast agents. Mr. [redacted] reports significant changes to his vision following his contrast agent overdose. Due to his contraindicated dosing of Conray, these persistent symptoms may likely reflect damage to relevant brain structures involved in ocular processes.

Cortical blindness is suggested to occur from the osmotic disruption of the BBB in the visual cortex subsequent to the injection of contrast product. (Mentzel, AJNR Am J Neuroradiol, 2003). Toxicity localized to the occipital lobes accounts for deficits in vision. Additional symptoms that may accompany cortical blindness include dysphasia, headache, seizure and memory loss (Boyes, Australas Radiol, 2000). The most compelling evidence for contrast-induced insult to the visual cortex is imaging work conducted within close temporal ranges to symptom manifestation using both CT and MRI. MRI imaging shows high signal intensities in occipital lobes 12 hours following contrast agent injection in a cerebral angiography procedure in a patient who developed subsequent cortical blindness. Repeat MRI conducted three days later did not illustrate these abnormalities and cortical blindness was resolved. The authors concluded that cortical blindness was a direct complication of the contrast agent (Suri, Ann Indian Acad Neurol, 2011). These reports are consistent with a review published on four cases of cortical blindness induced by contrast product following cerebral angiography. CT imaging was conducted in all four patients within one hour of contrast-injection and all patients demonstrated abnormal contrast enhancement in the occipital lobes of the brain. In addition, MRI imaging was conducted on two of the patients and revealed abnormal high signal intensity in the occipital lobes (Lantos, Neurology, 1989).

Re: Conray contrast agent overdose

Visual impairment may also occur with occipital seizures as an ictal or post-ictal phenomenon. Hadjikoutis and colleagues describe a patient who presented with headache, vomiting and bilateral visual loss. Persistent spike discharge was observed in the occipital lobes by EEG suggesting occipital seizures (Hadjikoutis, Neurology India, 2003). It is also known that iodine itself is a retinotoxic compound. High doses of iodate administered intravenously is toxic to the retina. Ocular toxicity is reported after exposure to doses ranging between 600-1200mg. It is possible that leakage of contrast agent to the retina could directly have impacted Mr. [redacted] vision.

Auditory Impairment



Cortical deafness is also a rare complication that has been associated with contrast agents. Cortical deafness refers to sensorineural hearing loss (partial or complete) caused by damage to the primary auditory cortex. Cortical deafness is rare and published reports are limited to case studies linking the symptom to injection of contrast agents. For example, severe bilateral sensorineural hearing loss following injection of iopamidol was observed following angiography. The patient did not respond to the nurse during the procedure and an auditory brainstem response test revealed no response in either ear even after click intensity was raised to 105 dB (Matsuoka, Acta Oto-Laryngologica, 1994). Similarly, another report describes sensorineural deafness in a patient following aortic angiography with iopamidol (Karim, AJKD, 2010). Experimentally, induced sensorineural hearing loss in gerbils demonstrates altered neuronal membrane potential, increased input resistance, higher instances of sustained neuronal firing and elevated thalamocortical and intracortical evoked excitatory synaptic responses (Kotak, J Neurosci, 2005). It is possible that exposure to high levels of contrast medium in the auditory cortex, located within the superior temporal gyrus of the temporal lobe, could damage neural tissue in this region thus leading to deficits in hearing.

Re: Conray contrast agent overdose

CONTRAST AGENT-INDUCED TOXICITY IN KIDNEY TISSUE

Brain biopsies and tissue histopathology are not the norm for severe contrast media toxicity. Aside from being clinically dangerous to do – an unnecessary risk to the patient – the findings do not assist in treatment. Again, no one disputes that ionic iodinated contrast media are neurotoxic. The exact mechanism escapes description because it hasn't been investigated and probably cannot be investigated. However, contrast media, as a chemotoxic, is toxic to cells in other vital organs in the body, organs which are subject to biopsy and removal and cellular histopathology. In those organs, in particular, the kidney, the cytotoxic effects are demonstrated and documented.

Systemic toxicity is known to occur with contrast agents. Contrast agents are potentially highly toxic to the renal system. Contrast-induced nephrotoxicity is well documented and considered by many the most important clinical challenge associated with these agents and the leading cause of contrast-mediated mortality, especially in patients with pre-existing renal dysfunction. Both acute and delayed renal complications are observed (Wang et al., Exp and Ther Med, 2016) (Homma, Keio J Med, 2016). Contrast-induced nephrotoxicity is responsible for 10% of hospital-acquired acute renal failure cases and is the third leading cause of renal function deterioration after decreased renal perfusion and postoperative renal insufficiency. Contrast-induced renal dysfunction has an increased mortality rate of 20% and long-term loss of kidney function is an observed complication (Levy et al., JAMA, 1996). The underlying mechanisms associated with contrast renal dysfunction appear to be a result of direct contrast-induced renal tubular epithelial cell toxicity and renal medullary ischemia in addition to changes in renal vasculature (Briquori et al., Prog Cardiovasc Dis., 2003). It is suggested that due to biological conditions within the kidney system, contrast agent media becomes concentrated in the tubules vessels increasing fluid viscosity and impeding flow. Reductions in flow rate increase contact of the contrast agent with the tubular epithelial cells and vascular endothelium, allowing for cytotoxic effects to occur. The generation of free radicals results in vascular changes and subsequent hypoxia.

Experimentally, cytotoxic effects are observed in a wide variety of cell lines *in vitro* following contrast agent exposure. Cultured cells, including endothelial and renal tubular cells, demonstrate significant cell damage and cell death after exposure to contrast agents (Sendeski, Clin Exp

Pharmacol Physiol, 2011). Iopamidol displays dose-dependent cytotoxic effects in rat mesangial cells and human fibroblasts. Mesangial cells play a critical role in renal function. Cell death in 50% of mesangial cells was demonstrated at 80 mgI/ml Iopamidol (Potier et al., Invest Radiol, 1997). Of note, there is currently no contrast agent devoid of cytotoxic efficacy and no contrast agent that does not induce clinical nephrotoxicity to some extent (Heinrich et al., Radiology, 2005). Cytotoxic effects *in vitro* are attributed to high concentration of iodine and subsequent iodine-induced toxicity (Lineaweaver et al., Plast Reconstr Surg, 1985). Photolysis in the cell frees iodine molecules from the contrast medium and even small amounts are potentially highly cytotoxic (Fanning et al., Br J Radiol, 2001).

The key point of the discussion is that contrast media are CYTOTOXIC – they kill cells. If enough of the cells are killed or damaged, the function of that cell or organelle, or region of the brain is damaged, and notoriously, brain tissue and function does not regenerate like many other systems in the body.

CONCLUSIONS AND OPINIONS

The neurotoxicity induced by Conray is multifaceted and caused by:

1) Increased permeability of the BBB mediated by the agent's hyperosmolarity and lipid solubility, (bypassed with intrathecal route here)
2) the agent's chemotoxicity,
3) relative dispersion of the agent in the spinal cord and brain parenchyma, and
4) Conray's intrinsic neurotoxicity.
5) Mr. [redacted] presents with significant medical complications including seizures, impairments in cognition and memory function, and disabling neuromuscular deficits following his toxic intrathecal exposure of Conray contrast product. Given the contraindicated dose that Mr. [redacted] received, the direct entry of the agent into the CNS, it is probable that significant and irreversible contrast neurotoxicity – death of brain and spinal cord cells -occurred and caused damage to neural tissue contributing to each of the neurologic and neuromuscular deficits.
6) The persistent damage to his cognition, memory, vision and hearing most likely originates from contrast-induced damage to brain structures involved in these processes, i.e., mesial

temporal, occipital and temporal cortical structures. The persistent damage to his sensory and motor capabilities most likely reflect damage to components of his spinal cord.

7) Given the chemotoxicity of the contrast agent, described to be caused by the intrinsic chemical nature of the contrast agent and the significant hyperosmolarity, the contraindicated dose and the direct exposure of the agent to the CNS during this procedure, it is highly probable that the adverse reactions, both transient and permanent, are contrast-induced chemotoxic reactions.

8) Mr. [redacted] was essentially neurologically intact before the contraindicated intrathecal injection (chemotoxicity) resulting in acute seizures and neuromuscular disability. A reasonable, clinically valid, and scientifically sound explanation of his current neurological deficits is the acute neurotoxicity, from which he did not fully recover.