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TOXIC MANIFESTATIONS OF CONTRAST AGENT OVERDOSE FOLLOWING MYELOGRAPHY

Stephanie E. Tedford*, PhD[1], James T. O'Donnell, PharmD, MS, FCP[1,2]

[1]*Pharmaconsultant Inc., Barrington, IL*
[2]*Rush Medical College, Department of Cell and Molecular Medicine, Chicago, IL*

Author Biography

James T. O'Donnell

Biography:
Dr. O'Donnell is an Associate Professor of Pharmacology at the Rush University Medical Center in Chicago, where he served as the Course Director for the Medical Pharmacology program. He also held Faculty appointments at the University of Illinois Colleges of Medicine and Pharmacy.
Dr. O'Donnell is a Diplomate of the American Board of Clinical Pharmacology, a fellow of the American College of Clinical Pharmacology, a fellow of the American College of Nutrition, Founding Editor-in-Chief of the Journal of Pharmacy Practice, and Editor of Drug Injury: Liability, Analysis, and Prevention, First Edition , Second Edition , Third Edition , and Co-editor of O'Donnell's Drug Injury Fourth Edition; a Co-Editor Pharmacy Law: Litigating Pharmaceutical Cases , and The Process of New Drug Discovery and Development, Second Edition , and co-editor of Drug Discovery and Development Third Edition. Dr. O'Donnell received a Bachelor of Science in Pharmacy from the University of Illinois, a Doctor of Pharmacy from the University of Michigan, and a Master of Science in Clinical Nutrition from Rush University.

Author Biography

Stephanie E. Tedford

Biography:
Dr. Stephanie E. Tedford, PhD is a neuropharmacologist with experience in a variety of academic, industry and legal settings. Dr. Tedford received a Bachelor of Science in Psychology and Neuroscience from Washington State University and a Doctor of Philosophy in Pharmacology from Rush University. Dr. Tedford graduated from Rush University with recognition and was awarded the Dean's Service Award and Paul E. Carson, M.D. Award for Excellence in Pharmacology. Dr. Tedford has held faculty positions at Rush University and Dominican University where she served as a member in the Neuroscience, Psychology and Pharmacology Departments. Dr. Tedford works in multidisciplinary roles within Medical and Scientific Affairs for industry, academia and legal practice.

*Corresponding Aurthor: Stephanie E. Tedford, Medical & Scientific Affairs, Clinical Operations, Independent Medical Writer, Austin, Texas, United States Email: setedford@gmail.com.

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Abstract

The administration of contrast media agents is relatively safe and rarely causes systemic toxicity in the course of routine imaging studies. While the incidence of serious toxicity is low, these drugs usually have fatal effects after Central Nervous System (CNS) exposure, when contraindicated, routes of administration allowing CNS or spinal cord entry, and in doses that exceed user recommendations. Most patients do not survive overdose effects, and therefore, limited information exists on long-term sequelae following such incidents. We provide evidence for the acute and chronic effects of exposure to contrast media overdose in two patient cases. We report findings from inadvertent overdose following administration of iopamidol and iothalamate resulting in the manifestation of serious and persistent adverse effects. Expertise in assessing adverse drug reaction reports is an essential and required responsibility of drug developers and regulators.

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Introduction

Myelography is a type of radiographic imaging used to assess the integrity of the spinal canal. A myelogram test provides insights into abnormalities of the spinal cord that may be underlying clinical deficits. This assessment is useful for visualizing bones, herniated discs, and other soft tissues surrounding the spinal canal that may be compressing the nerves and/or spinal cord. Contrast agents are administered prior to imaging to enhance structure resolution. A number of different contrast media agents with various toxicities are used in myelography [1, 2]. Iodinated contrast agents are commonly employed and are considered to be generally safe and effective when administered correctly. Iodinated contrast agents are most frequently administered through intravascular injection, but due to the pharmacokinetic properties of the compound, the agent quickly redistributes to the extravascular space [1, 3]. While rare, contrast-induced toxicity can result in serious complications that can be life-threatening [4-9]. Dosing and administrative errors contribute to an increased risk for toxicity. Contrast toxicity presents in a myriad of ways. While not fully understood, each manifestation often has several likely underlying mechanisms. There is scant information detailing outcomes and side effects of contrast agent overdose other than death since most patients do not survive. In this report we provide evidence from two patient cases on the acute and chronic effects of exposure to contrast media overdose.

Case I

A 62-year-old woman was inadvertently administered an intrathecal overdose of iopamidol (Isovue-M), an iodinated contrast, agent while undergoing a total columnar myelogram. The manufacturers recommend a 10 ml injection of iopamidol (300 mg/ml iodine) for a dosing range of 2,000-3,000 mg iodine in adults. The patient was administered 22 ml of Isovue-M for a total administered dose of 6,600 mg iodine. The dose administered was 2-3 times the recommended maximum dose for the myelogram procedure. Following the procedure, the patient developed altered cognitive function, memory loss, and seizure activity within several hours during her hospitalization and upon discharge was released with ongoing medical problems including “altered mental status”, “contrast-induced seizures” and “status epilepticus”. A head CT performed 18 hours post-procedure showed iopamidol in the subarachnoid spaces, and CT density readings of the cerebral spinal fluid (CSF) were 829 HU (Hounsfield unit), which is over 200 times higher than normal CSF CT density scores. Moderately high iodine contrast content in CSF was still observed in the aspirate two days later. Following the procedure, the patient experienced mental disorientation, seizure activity and memory loss within 5-6 hours during her hospitalization
Prior to the patient’s unintentional exposure to iopamidol, she was neurologically intact with no reports of the deficits described following the event. Following the overdose, the patient continued to experience significant medical complications, including cognitive deficits, seizure activity, impairments in memory function, and significant hearing loss.

Case II

A 45-year-old man was inadvertently administered an intrathecal dose of iothalamate (Conray contrast product), an iodinated contrast media agent while undergoing a myelogram procedure. 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 administration, the patient immediately exhibited signs of contrast-induced neurotoxicity, including lower limb disturbances, seizure activity, cognitive dysfunction, and memory loss. He also presented with peripheral paraesthesia, bilateral lower extremity tingling, and spasms. It was quickly determined that he had been administered the incorrect contrast product for intrathecal use in myelography; iothalamate 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. The patient was also treated transiently with Keppra to control his seizure activity. The patient was released four days following the procedure.

Prior to the patient’s unintentional exposure to iothalamate, he was a neurologically sound individual whose primary complaint was for symptoms of vertigo. Following the overdose event, the patient continued to experience persistent cognitive impairment, including the inability to concentrate, inability to multitask, dull tension-like headaches, and blurriness of vision. He also exhibits neuromuscular impairments such as diffuse hyperreflexia, dizziness, vibratory paraesthesia, unsteadiness, generalized weakness, and intermittent muscle spasms.

Discussion

A pharmacologist who reviewed the cases opined that both patients suffered an overdose of their respective iodinated contrast agent, and the symptoms experienced were caused by contrast-induced toxicity. The chronic effects experienced by both patients stemming from this overdose can be attributed to sustained damage to various tissues exposed to the contrast agent. Both product inserts for iopamidol and iothalamate warn against the entry of a large or concentrated amount of the contrast medium into the brain, which can increase the risk of neurotoxicity. The medication errors that occurred in both cases resulted in the Central Nervous System (CNS) being exposed to excessive amounts of contrast agent. The pathological underpinnings that drive these adverse effects are uncertain. We provide potential support for the posed underpinnings below.

Mechanisms for cerebral (neurotoxic) injury

The exact mechanisms underlying cerebral insult following contrast agent administration remains uncertain. Several mechanisms of cellular neurotoxicity on selected regions of the brain affecting cognition, memory, hearing, and vision are described. The entry of the contrast agent into the brain parenchyma is attributed to the breakdown of the blood-brain barrier (BBB). BBB disruption can be explained by the hyperosmolarity and chemotoxicity of iodinated contrast agents [6]. Experimentally, the BBB will open upon exposure to hypertonic solutions [10]. Contrast agents generally possess significantly higher osmolarity than plasma, blood, and CSF; this 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 uncoupling of tight junctions and enhanced endothelial pinocytosis, thereby allowing for entry of the contrast agent. Alternate theories include prolonged exposure of the contrast agent with the endothelium associated with extended bolus transit time.

The severity of the barrier dysfunction is proportional to the relative chemotoxic action of the respective contrast agent. Upon entry of the contrast medium into the cranial subarachnoid space, it permeates the extracellular space by passive diffusion through the pia mater. Exposure of high doses of iodine to brain tissue can induce a severe disruption in cellular functions, including changes in a neural transmission and cell death. Altered neuronal membrane permeability and depolarization properties of neurons may contribute to dysfunctional neuronal communication. Changes in neurological activity such as the development of seizures, amnesia, and cortical ocular/auditory deficits occur when nonionic contrast products penetrate the brain. The entry of the contrast agent into the brain can result in profound neurotoxicity and serious complications. Contrast media neurotoxicity can mimic subarachnoid hemorrhage in a variety of imaging procedures [11-13]. The neurotoxic

effects are generally considered self-limiting and reversible however, case reports exist that detail prolonged neurological deficits similar to the patient cases in the present report [14].

Contrast-induced adverse reactions are categorized as chemotoxic or idiosyncratic reactions. Chemotoxic reactions are related to the physicochemical properties of the contrast medium and dosing parameters. Pharmacodynamic properties of the contrast agent on tissue are included in this category. The incidence of electroencephalographic changes by virtue of the intrinsic properties of the compound molecule underlies the neurotoxic effects of these agents. The brain is a homeostatic organ, and changes in osmolarity due to the hypertonicity of the contrast product may not only disrupt the BBB but in severe instances, may cause widespread osmotic changes in the brain sufficient to induce global cell death. There are many case studies that detail contrast agent-mediated complications. A review conducted by Spina et al. found 52 reports of contrast-induced encephalopathy (CIE) following cardiac catheterization [5]. Encephalopathy, motor, sensory and visual disturbances, ophthalmoplegia, aphasia, and seizures were most commonly reported. Cortical blindness is the most commonly reported neurological syndrome, occurring in almost 50% of cases.

One case study 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. Imaging from the CT also revealed increased density in the cerebral cortex, basal ganglia, and thalamus consistent with the localization of the existing intracerebral agent. The patient succumbed to the cerebral insult 48 hours post-contrast injections. A CT confirmed high concentrations of the contrast agent still present in the patient at the time of death. In addition, 4 hours post-mortem an iodine assay by fluorescence excitation revealed extremely high iodine concentrations throughout the brain. The concentrations observed in the cortical, thalamic and hippocampal regions were significant. 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 exceeded the maximum recommended dose [7]. 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 [8]. This report demonstrates the potential of serious contrast-induced disturbances even within a normal dosing protocol.

Therefore, significant changes in the osmolarity of the brain may contribute to leakage of the contrast product across the BBB. In addition, profound changes can induce considerable brain edema, which may be detrimental to brain function. In patient case 1, the BBB was bypassed by an intentional direct intrathecal injection. The overdose and the maneuver to move the contrast media to the cervical vertebrae caused the brain to be showered with neurotoxic, chemotoxic, hyperosmolar chemicals – poisonous to brain tissue.

Contrast-induced neurological and cognitive deficits

Both patients from Case 1 and 2 immediately developed prolonged seizure activity along with acute and sustained deficits in cognition and memory function. A review of the US FDA MedWatch reporting database (conducted September of 2016) lists 676 cases of adverse reactions related to cognitive impairment, seizures, and amnesia with nonionic radiographic contrast agents. There is substantial evidence for the development of seizures following the administration of iodinated contrast agents. Although epileptic seizures are a rare occurrence (typically observed in <1%), they are a well-documented complication. 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 shows high levels of remaining contrast in the brain and enhancement in cortical brain regions [15]. Preclinical studies report that administration of contrast agents are epileptogenic when directly exposed to brain tissue in rabbits [16] and rats [17]. 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) [18]. While the precise mechanisms underlying seizure induction are not known, it has been suggested that contrast-mediated changes in neural activity within subcortical circuits induce seizures at the thalamic level and cause disruptions in thalamocortical communication [18]. The neural circuits involved in seizures are acutely and may be permanently altered structurally and functionally following a seizure episode. Englot and Blumenfeld's theory states that focal seizures spread to the thalamus, disrupting corticothalamic interactions. 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 [19].

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 [20]. 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 [21]. Electrically-induced convulsive seizures disrupt spatial learning and also reduce LTP processes in the hippocampus [22]. In humans, reductions in LTP are observed in epileptic focal regions located in the hippocampus [23]. The accumulated evidence suggests that seizures can impact 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 in both these case reports 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 processes 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 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 [17, 24]. Reports of amnesia associated with contrast agents' dates back to the 1950's [25]. These effects can be permanent or transient and typically appear in the onset within hours of contrast agent injection. The US FDA MedWatch reporting database (conducted September of 2016) 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 is a recognized substrate for permanent amnesia [26]. Adults with a diagnosis of temporal lobe epilepsy display deficits in memory function [27]. 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 the 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 [28]. More specifically, CA1 (cornu ammonis) located within the hippocampus are critical for the retrieval of both short and long-term memory [29]. Contrast agents induce excitatory changes in neurons and dose-dependent obliteration of recorded electrical activity in rat hippocampal slices [17].

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 psychometric testing following myelogram procedures with contrast agents metrizamide and iopamidol. Mild mental deficits were observed following metrizamide administration. The severity of cognitive impairment was dependent on the quantity of contrast medium diffusion delivered into the intracranial space, suggesting dose-related neurotoxicity [30]. Contrast-related effects targeted to the frontal lobe may be responsible 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. Thus, neurotoxicity in the frontal and temporal lobe structures (e.g., the 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 rats, a process commonly associated with medial temporal brain structures (i.e., hippocampus) [31]. 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 [32]. Ischemia-induced damage to neural structures may contribute to the symptoms exhibited by both patients following contrast agent overdose.

Contrast-induced visual and auditory impairment: Further evidence for cerebral insult to cortical brain structures

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 US FDA MedWatch database (conducted September of 2016) reports a minimum of 66 adverse events associated with ocular disturbances, including reductions in visual acuity and blindness following injection of contrast agents. Spina et al. report that transient cortical blindness is the most commonly reported neurological syndrome in patients that experience CIE (contrast-induced encephalopathy), occurring in approximately 50% of cases [5]. Significant changes to vision following contrast agent overdose probably reflect damage to 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 products [33]. 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 [34]. The most compelling evidence for the contrast-induced insult to the visual cortex is imaging work conducted within close temporal ranges to symptom manifestation using both CT (computerized tomography) and MRI (magnetic resonance imaging). 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 [35]. 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 [36].

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 [37]. It is also known that iodine itself is a retinotoxic compound. High doses of iodate administered intravenously are toxic to the retina. Ocular toxicity is reported after exposure to doses ranging between 600-1200mg [38]. It is possible that leakage of contrast agent to the retina could directly impair vision [39].

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 [40]. Similarly, another report describes sensorineural deafness in a patient following aortic angiography with iopamidol [41]. 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 [42]. 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.

Conclusions

The patient case reports and relevant literature detail the serious acute

and residual toxicity following an overdose of contrast agents used for myelogram procedures. The damage to neurological functions (e.g., cognition, memory, motor, vision, and hearing) likely originates from contrast-induced damage to brain structures involved in these processes, i.e., mesial temporal, occipital and temporal cortical structures. It is established that contrast agents are chemotoxic due to the intrinsic chemical nature and significant hyperosmolarity. Given the chemotoxicity of the contrast agents, contraindicated route of administration, excessive dose and penetration of the agent into the CNS during these procedures, it is highly probable that the adverse reactions experienced by the patients in the case reports are contrast-induced chemotoxic reactions. Both patients were essentially neurologically intact before the contrast agent overdose. While commonly employed in imaging procedures, extreme caution should be taken to avoid medication errors with contrast agents to avoid toxicity.

Disclosures

James T. O'Donnell served as an expert witness for the patients described in both cases reported in this manuscript.

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