

Severe and Prolonged Symptoms after Intrathecal Administration of Gadobutrol (Gadovist®)

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Objective

Gadolinium-based MRI contrast agents are widely used for various diagnostic procedures and are approved for IV use only. A crucial adverse effect is nephrogenic systemic fibrosis (NSF), whereas CNS toxicity is usually low. (1)

In a patient with renal failure, gadolinium-induced encephalopathy developed after repeated IV doses of gadolinium over 7 days. (2)

Encephalopathy after inadvertent entrance of gadolinium into the intrathecal compartment is a known complication and can cause a variety of neurologic symptoms. (3)

Requests regarding these group of drugs are rather uncommon, and usually previously described adverse reactions occurred.

We report on a case with severe and prolonged neurological symptoms following intrathecal misapplication of gadobutrol (Gadovist®).

Case series

Between October 1996 and October 2016, a total of 11 exposures to gadolinium-based MRI contrast agents were reported to the Poisons Information Centre (PIC) Erfurt. In 5 cases (45.5 %) adverse reactions with therapeutic use were observed, in 3 cases (27.3 %) the patient was administered the wrong dose, and in one case (9.1 %) extravasation occurred. There was also one case (9.1 %) of accidental exposure, when the agent splashed into the eye of a doctor. A case (9.1 %) of intrathecal misapplication is described below.

Case report

A 53-year-old female received 10 mL of gadobutrol (Gadovist®) intrathecally during a diagnostic procedure at the lumbar spine. She immediately developed severe pain and seizures, showing a prolonged epileptic activity in EEG. Contrary to the PIC's advice, cerebrospinal fluid lavage was not performed. The patient was sedated and treated with analgetics plus anticonvulsives as well as high-dose glucocorticoids (methylprednisolone 1 g/d). However, even analgosedation could not suppress epileptic activity within 4 days. After 18 days, the patient still showed neurological impairment. Within two months after exposure, the patient's condition gradually improved, and she was then transferred to a rehabilitation facility. Yet, long-term damages still cannot be ruled out completely.

Intrathecal toxicity of gadobutrol

Inadvertent intrathecal administration of another gadolinium-based MRI contrast agent (gadopentetate dimeglumine) has been reported to cause confusion, nausea, vomiting, ataxia, nystagmus, hallucinations, blurred vision, and a depressed mental status in a 64-year-old male. In this case, the patient still showed slight neurological deficits 56 days after application. Symptoms were referred to as gadolinium-induced encephalopathy. (4)

In general, intrathecal misapplication of xenobiotics can cause disruptions of normal neurotransmission and toxicity due to physicochemical properties such as ionization, hyperosmolarity, and lipophilicity. Typical symptoms, regardless of the xenobiotic, are pain, paraesthesias, instability of blood pressure, and hyperreflexic myoclonic spasms as well as seizures and depressed levels of consciousness. (5)

Management of intrathecal gadobutrol poisoning

Treatment is mainly symptomatic and includes sedation, analgetics, assisted ventilation, and anticonvulsives, as well as high-dose glucocorticoids for cerebral protection. (3) Especially for xenobiotics with uncertain and potentially fatal outcomes, cerebrospinal fluid lavage is recommended within one hour after exposure. (5)



Fig. 1 – Gadovist® (<https://www.radiologie-shop.bayer.de/kontrastmittel/mr-kontrastmittel/gadovist>)

Conclusion

Gadolinium-induced encephalopathy has been reported in several cases and only recently, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended the suspension of the marketing authorisations for four linear gadolinium contrast agents (gadobenic acid, gadodiamide, gadopentetic acid, and gadoversetamide) because of evidence that small amounts of the gadolinium they contain are deposited in the brain. (6)

Yet, gadolinium may not be the culprit in our case. Instead, we assume that the high quantity (10 mL) and high osmolarity (1 mmol/mL) of the applied mixture could have induced a physicochemical imbalance of cerebral fluids, leading to irritation of the meninges followed by the above-mentioned symptoms. Although cerebrospinal fluid lavage has not been evaluated for cases of gadolinium misapplication, it has successfully been applied for intrathecal vincristine poisonings, and may have been beneficial in this case, too.

References

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- (5) Goldfrank's Toxicologic Emergencies, Ninth Edition, McGraw-Hill 2011
- (6) PRAC concludes assessment of gadolinium agents used in body scans and recommends regulatory actions, including suspension for some marketing authorisations (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Gadolinium-containing_contrast_agents/human_referral_prac_000056.jsp&mid=WC0b01ac05805c516f)