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REVIEW ARTICLE

Safety of intrathecal route: focus to methylprednisolone acetate (Depo-Medrol) use

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Abstract

Purpose Complications of the intrathecal route may cause potential toxicity related to the medical device and properties of the administered drug and/or excipient. A description of clinical and histological effects of polyethylene glycol and miripirium after Depo-Medrol injection, and the adverse reactions of particulate methylprednisolone acetate was conducted. The safety of the intrathecal route with excipients, label and off-label drugs is discussed.

Methods A bibliographic search in Medline, Google, and Cochrane database from 1940 to June 2016 was performed. The keywords included 'intrathecal methylprednisolone acetate', 'miripirium', 'myristyl-gamma-picolinium', 'side effects', 'intrathecal Depo-Medrol', 'polyethylene glycol', and 'intrathecal devices' used individually or in combination.

Results Adverse reactions have been reported with this intrathecal administration route such as arachnoiditis, bladder dysfunction, headache, meningitis. Some pharmaceutical excipients have been associated with specific toxicity issues and with allergic and anaphylaxis reactions. Additives of methylprednisolone acetate formulations such as polyethylene glycol and miripirium chloride can be neurotoxic when injected intrathecally. Polyethylene glycol—an antimicrobial agent widely used in pharmaceutical drugs—has been associated with cardiovascular, hepatic, respiratory, and CNS toxicity.

Conclusions Intrathecal methylprednisolone acetate (Depo-Medrol) therapy seems not fully safe due to reported adverse events. The use of other forms of corticosteroid therapy free from excipients should be emphasized such as soluble methylprednisolone sodium succinate.

Keywords Drug safety · Intrathecal injection · Methylprednisolone acetate · Off-label

Introduction

Intrathecal (IT) drug delivery has been available since the 1980s to manage mainly central nervous system (CNS) cancer, chronic intractable pain, and spasticity [1, 2]. The objective of the IT route is to improve CNS drug exposure in the cerebrospinal fluid (CSF) and to reduce the risk of systemic drug toxicity [3]. The IT chemotherapy help to circumvent the brain drug distribution limitations imposed by the blood–brain barrier after systemic drug administration. However, the IT route can cause some specific complications related to medical device issues and properties of the drug and/or excipent administered into the CSF [4]. The introduction of a catheter into the CSF space is prone to mechanical complications such as leak, break, tearing, kinking, obstruction, dislodgment, or disconnection [5, 6]. These complications can be associated with spinal headaches, neurologic injury, or subdural hygroma [7]. Also infectious risks related to IT procedures may represent indirect complications like superficial wound infections, epidural abscess, and infectious meningoencephalitis [7, 8]. Neurotoxicity has been also reported including acute chemical arachnoiditis, seizures, spinal cord lesions, and encephalopathy possibly leading to deapth [4, 9, 10]. The most common medications delivered by IT route were baclofen, methotrexate, cytarabine, and corticosteroids

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[4]. More recently, the IT route gains further interest for novel off-label therapies unable to reach significantly the brain parenchyma by systemic administration like monoclonal antibodies which are proposed in some CNS autoimmune disorders and cancers [11, 12]. Care must be taken with medications administered by the IT route because of the clinical consequences which are potentially fatal [4, 13, 14]. IT administration for off-label drugs is crtitical and should not contain IT incompatible excipients. Few data support the safety of IT injection for off-label drugs and excipients but the inocuity for some compounds still need further investigations. The aim of this work was to make a focus on the IT safety for excipients and the off-label IT methylprednisolone acetate (MPA) administration.

Methods

A bibliographic search in databases including Medline, Google, and Cochrane from 1940 to June 2016 was performed. The keywords terms included 'intrathecal methylprednisolone acetate', 'miripirium', 'myristyl-gamma-picolinium', 'side effects', 'intrathecal Depo-Medrol', 'polyethylene glycol', and 'intrathecal devices' and they were used individually or in combination. Articles were excluded if they were written in a language other than English. The search and selection of articles were performed by Pharm D and/or Ph D and qualified Pharm D responsible for post-marketing surveillance. All articles were evaluated by two or more authors checking the authority, accuracy and currency. The scientific credibility of articles was checked by the expertise and affiliation of authors, and the scholarly or peer-reviewed source. The accurate information of articles was determined by stating the facts with references and information reports. The currency was evaluated by the evidence of updated information. At any time, the pharmaceutical companies were involved in this study.

Results

Intrathecal drugs use and potential side effects of excipients

Available label and off-label therapeutic drugs used by IT route are reported in Table 1. Table 2 reports the main excipients implicated in IT toxicity. The university hospitals of Paris (Assistance Publique des Hôpitaux de Paris—APHP) have published some recommendations for the safety use of the IT administration of drugs summarized in Table 3.

Methylprednisolone acetate

Methylprednisolone acetate (MPA) has a long history of use in the treatment of neuropathic pain syndromes. In the early 1960s, MPA began to be used in the management of spinal pain states [15, 16]. More recently, MPA has been used to treat intractable postherpetic neuralgia in patients that remain refractory to the current therapies and continue to have severe burning and lancinating pain [17–19]. Moreover, IT MPA administration has become a rationale treatment for acute lymphoblastic leukemia (ALL) [20–22]. Acute leukemia is the most frequent cancer in childhood (33%) with 80% of ALL [23]. Major progress has been made in the management of ALL and most pediatric patients now survive for long periods. Patients are included in clinical trials conducted by groups of investigators, such as the Children' Oncology Group in the United States, the United Kingdom ALL, and French ALL groups [24]. In the French ALL protocol, treatment usually includes an initial phase following by maintenance/relapse therapy [25, 26]. To prevent meningeal relapse, as CNS is a possible sanctuary for lymphoblast, prophylaxis treatment is currently based on IT chemotherapy with triple mixture: methotrexate, cytarabine, and corticosteroid [21, 22, 27]. Reports have demonstrated that triple IT therapy decrease CNS relapse and boost the event-free survival rate and could reduce the use of cranial irradiation therapy [27–29]. A recent study noted in children treated with triple IT therapy alone a 5-year overall survival rate of 90.6%. The 7-year cumulative risk of any CNS relapse was evaluated at 1.4% [29]. In the French ALL protocol, the MPA such as 40-mg/ml Depo-Medrol injection form is widely used off-label by IT administration to pediatric patients. This dosage form contains excipients such as polyethylene glycol and miripirium that have been shown to cause adverse effects.

Intrathecal MPA side effects

The IT treatment with MPA (Depo-Medrol) was first described in 1961 by Gardner et al. from patients with sciatica and later in patients suffering from sclerosis [30]. MPA is used mainly in rheumatology by intra-articular administration to treat arthritis, tendonitis, or bursitis. IT MPA injection (20–80 mg) is used off-label for the treatment of neuropathic diseases and acute lymphoblastic leukemia (ALL). However, potential complications of the IT MPA administration were reported questioning its IT use. In few publications, complications included cases of arachnoiditis, aseptic meningitis, neurologic worsening, and subarachnoid hemorrhage from patients with

Table 1 Label and off-label drugs administered intrathecally

Label drugs	Strength	Excipients	Indications
Baclofen (Lioresal intrathecal)	0.05, 0.5, and 2 mg/ml	Sodium chloride 0.9% in water for Injection; pH 5.0–7.0	Management of severe spasticity
Ziconotide acetate (Prialt)	25 and 100 mcg/ml	L-Methionine and sodium chloride; pH 4.0–5.0	Management of severe and chronic pain
Methotrexate sodium preservative free	25 mg/ml	Sodium chloride 9.8 mg, sodium hydroxide qs pH 8.5, water for injection	Neoplastic diseases
Cytarabine (Depocyt)	10 mg/ml	Cytarabine liposomes in 0.9% w/v sodium chloride in water for injection Each ml contains 10 mg cytarabine, 4.4 mg cholesterol, 1.2 mg triolein, 5.7 mg dioleoylphosphatidylcholine (DOPC), and 1.0 mg dipalmitoylphosphatidylglycerol (DPPG)	Intrathecal treatment of lymphomatous meningitis
Bupivacaine (Marcaine)	0.25 and 0.5%	Sodium hydroxide to pH 5.4–5.6 and water for injection	Local anesthetics
Choroprocaine (Clorotekal, Nesacaine)	10 mg/ml	Sodium chloride, sodium chloride 1 N to pH 3–4, water for injection	Local anesthetics
Levobupivacaine (Chrocaine, Levobuki)	2.5 and 5.0 mg/ml	Sodium chloride 9 mg/ml, water for injection, sodium hydroxide and/or hydrochloric acid to pH 4–6	Local anesthetics
Prilocaine (Baritekal)	20 mg/ml	Glucose 60 mg/ml, sodium hydroxide to pH 4–6, water for injection	Local anesthetics
Ropivacaine	5 mg/ml	Sodium chloride, water for injection, sodium hydroxide and/or hydrochloric acid to pH 4–6	Local anesthetics
Morphine preservative free	1, 10, and 20 mg/ml	Sodium chloride, water for injection, hydrochloric acid to pH 3–4.5	Narcotic analgesic
Buprenorphine (Temgesic, Buprenex)	0.3 mg/ml	Glucose, hydrochloric acid, water for injection	Narcotic analgesic
Asparaginase (Kidrolase)	10,000 UI	Glycine, sodium hydroxide to pH 6.8–7, water for injection	Neoplastic diseases
Prednisolone (Hydrocortancyl)	2.5%	Benzyl alcohol 0.9 g/100 ml, sodium carmellose 0.3 g/100 ml, sodium chloride 0.8 g/100 ml, polysorbate 80 0.4 g/100 ml, water for injection	Corticoids
Amikacine Mylan	50, 250, 500, and 1000 mg	Sodium hydroxide to pH 6.5, water for injection	Antibacterial
Colymicine (Sanofi)	1 MUI	Powder	Antibacterial
Iopamidol (Iopamiron)	Iodine 200 and 300 mg/ml	Tometanol, sodium edetate calcium, hydrochloric acid, sodium hydroxide to pH 7.3, water for injection	Contrast agent
Iohexol (Omnipaque)	Iodine 140, 180, 240, 300, 350 mg/ml	Each milliliter contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide	Contrast agent

Table 1 (continued)

Label drugs	Strength	Excipients	Indications
Iodixanol (Visipaque)	Iodine 270 and 320 mg/ml	Trometanol, sodium chloride 0.187 g/100 ml, calcium chloride, calcium edetate sodium, hydrochloric acid to pH 7.2–7.6, water for injection	Contrast agent
Iométrol (Iomeron)	Iodine 200, 250, 300, and 350 mg/ml	Trometanol, hydrochloric acid, water for injection	Contrast agent
Off-label drugs	Strength	Excipients	Indications
Trastuzumab (Herceptin)	440 mg	20 ml of water for injection containing 1.1% benzyl alcohol In patients with known hypersensitivity to benzyl alcohol, 20 ml of water for injection	HER2 receptor antagonist (Gulia et al. [60])
Rituximab (Rituxan)	10 mg/ml	Tween 80 (0.7 mg/ml), sodium chloride (9 mg/ml), sodium citrate dihydrate (7.35 mg/ml), water for injection. The pH is 6.5.	CD20-directed cytolytic antibody (Doorduijn et al. [61], Bonnan et al. [12])
Dexmedetomidine	100 mcg/ml	Sodium chloride, water for injection, pH 4.5–7	Central alpha-2 adrenergic agonist (Safari et al. [62])
Fluorescein	Dye	5% sodium fluorescein dye diluted with cerebrospinal fluid (CSF) or 9.9 ml of CSF diluted with 0.1 ml of 10% fluorescein or 25 mg fluorescein diluted in 10 ml CSF	Tracer for angiography and diagnosis (Tandon et al. [63], Antunes and Perdigão [64], Raza et al. [65])

sclerosis receiving IT MPA (40–120 mg) [31, 32]. Bernat et al. reported a case of sclerosing spinal pachymeningitis complicating the IT MPA administration (12 injections at 80 mg) [33]. Authors concluded that IT MPA produced meningeal irritation and the vehicle is the necrotizing fraction. Another subsequent reports concluded that patients developed clinical signs of arachnoiditis after one single or multiple MPA injections [34, 35]. More recently, a randomized control trial was conducted in ten postherpetic neuralgia patients to compare the clinical effects between IT mixture of MPA 60 mg and lidocaine 60 mg and IT lidocaine 60 mg alone (control) [36]. The MPA-treated patients experienced more pain with a pro-inflammatory interleukine-8 CSF level significantly increased after the first MPA injection as compared to the control group. The authors did not recommend IT MPA administration considering the lack of clinical effects and toxic risks of the treatment. Two studies aimed to assess the toxicological and histological effects of IT MPA administration in dogs demonstrated that the IT causes histological changes on the animals studied [37, 38]. First study of safety assessment of IT MPA in dogs reported the dose-dependant IT inflammatory reaction of MPA doses [38]. Seventeen dogs were randomized in three groups receiving lidocaine (4 dogs), MPA 20 mg/ml (7 dogs), or MPA 80 mg/ml (6 dogs). The group with MPA at 20 mg/ml had a diffuse inflammatory reaction whereas the group with MPA 80 mg/ml present a severe inflammatory response histologically confirmed. A second study assessed the safety of IT MPA in dogs which were assigned in two groups: IT with saline solution (group 1) and group 2 receiving IT MPA 1.15 mg/kg [37]. In group 2, dogs exhibited histological changes such as meningeal thickening and lymphocytic infiltrations. In three animals, adhesion of pia, arachnoid, and dura matter was noted and a necrosis of the spinal cord in one animal was observed.

Commercial MPA (Depo-Medrol) and preservatives

MPA pharmaceutical forms (Depo-Medrol) are sterile aqueous suspensions approved as an anti-inflammatory glucocorticoid for intramuscular, intra-articular, soft tissue, or intralesional injection. Two different formulations are commercially available by Pfizer (e.g. single or multi-dose formulation) with the same denomination: Depo-Merdol (Table 4). In the United States, the two Depor-Medrol commercial forms are not indicated for IT administration because they have been associated with severe medical events hence administered by IT route [39]. Only the second formulation (single-dose) is available in France without contraindications for IT injection. Therefore, it is used off-label in ALL protocol by the IT route in association with methotrexate and cytarabine.

Table 2 Noticeable effects of excipients by intrathecal use

Excipients	References	Noticeable effects (references)
Benzyl alcohol	Saiki et al. [66]	Paraplegia following intrathecal chemotherapy with methotrexate and cytosine arabinoside in 13-year old girl (total dose exposure was 1035 mg)
	DeLand [67]	Aseptic meningitis following intrathecal administration of radiopharmaceuticals containing benzyl alcohol in dogs (transient respiratory arrest with 90 mg in 7 adult dogs, death with 18 mg in 2 immature dogs)
	Craig and Habib [68]	Severe flaccid paraplegia after epidural anesthesia in a 24-year-old primagravida (1.5% benzyl alcohol in 0.9% saline injection)
	Niv et al. [69]	Decrease (80–90%) in the sympathetic responses after intrathecal administration of commercial midazolam hydrochloride containing 5 mg/ml of drug and 10 µl per ml of benzyl alcohol
	Hahn et al. [70]	Flaccid paraplegia after intrathecal injection of cytosine arabinoside diluted in 1.5% benzyl alcohol in water. In acute and chronic animal experiments, benzyl alcohol in commercially used concentrations can have a toxic effect on nerve fibers
Phenol	Swerdlow [71]	Retention of urine (8), numbness (4), headache (2), paralysis of rectal sphincter (3), paresthesia (2) after intrathecal injection of phenol 5–7% in glycerin in 46 patients
	Du Pen et al. [72]	Confusion and disorientation after chronic intrathecal administration of methotrexate containing 2.5 mg of phenol and 2.8 mg of formaldehyde in each ml in a 23-year-old patient
	Rincon et al. [73]	Giant spinal arachnoid cyst after intrathecal injection of phenol in 36-year-old woman
Formaldehyde	Du Pen et al. [72]	Confusion and disorientation after chronic intrathecal administration of methotrexate containing 2.5 mg of phenol and 2.8 mg of formaldehyde in each ml in a 23-year-old patient
Chlorocresol	Swerdlow [71]	Retention of urine (9), numbness (9), paresis (3), headache (3), paralysis of rectal sphincter (2), paresthesia (1) after intrathecal injection of chlorocresol 1:50 or 1:40 in glycerin in 42 patients
Chlorobutanol	Malinovsky et al. [74]	Lesions in both histologic and blood–brain barrier after intrathecal injection of 0.05% chlorobutanol in rabbits (hemorrhage and necrosis in gray structures in 60% of the spinal cord slides)
Parabens (methyl and propyl)	Saiki et al. [66]	Paraplegia following intrathecal chemotherapy with methotrexate and cytosine arabinoside in 13-year-old girl (total dose exposure of methylhydroxybenzoate and propylhydroxybenzoate was 6.4 and 1.6 mg, respectively)
	Gurun et al. [75]	No neurotoxicity from intrathecal injection of neostigmine containing 1.5 mg/ml methylparaben, and 0.2 mg/ml propylparaben in rats and sheep
Sodium bisulfite	Wang et al. [76]	Irreversible hindlimb paralysis in rabbits after intrathecal injection of 1.2–2.4 mg sodium bisulfite
	Ready et al [77]	Histologic lesions after intrathecal injection of sodium bisulfite added in local anesthetic agents in rabbits (cauda equine at 0.1% level, cauda equine and central necrosis at 0.4 and 0.8% levels)

Table 3 Recommendations for the safety use of intrathecal administration of drugs

General	Drug as far as possible must not contains any potential toxic excipients The pH of intrathecal solution must be ranged from 4 to 8, and preparation should be iso-osmolar The preparation of intrathecal injections must be protocolized and achieved by trained personnel If the preparations are realized in central pharmacy, there are delivered individually by patient in secured box
Medical devices	Not to confuse spinal anesthesia needle with epidural needle Use needle with not edge bevel and diameter equal or greater than 22G Use small volume syringe specifically labeled differing from intravenous or subcutaneous syringe
Anesthesia and intensive care unit	In case of deconditioning of injectable solutions, use wells of different colors Deconditioning exposes to the risk of injecting colorless solutions like hypertonic sodium chloride or chlorhexidine, cause of tetraplegia Pay attention to inversion between drugs for the intravenous route and drugs for intrathecal route Pay attention to overdoses (dose calculation, strong control of pump…)
Oncology	Pay attention to simultaneous administrations of intravenous and intrathecal cytotoxic drugs - avoid IT injection the day of vinca alakaloids intravenous administration Prepare the vinca alkaloids (vincristine…) in small volume bags exclusively to avoid their administration by the IT route Identify clearly the intrathecal route on the cytotoxic prepared only in syringe Never give intrathecally a colored solution (daunorubicin, doxorubicin, mitoxantrone) excepted the yellow methotrexate solution
Infectious	Pay attention to inversion between intravenous and intrathecal antibiotics
Radiology	Ionic contrast agents are formally contraindicated by intrathecal route

Table 4 Commercially available formulations of Depo-Medrol

Excipients	Multi-dose formulation (mg)	Single-dose formulation (mg)
Polyethylene glycol 3350	28.2–29.5	28–29
Tween	1.88–1.97	None
Monobasic sodium phosphate	6.59–6.90	None
Dibasic sodium phosphate USP	1.37–1.44	None
Benzyl alcohol	8.88–9.30	None
Myristyl-gamma-picolinium chloride (miripirium)	None	0.189–0.195

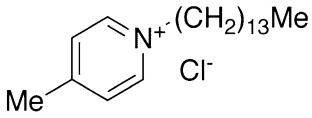

Fig. 1 Chemical structure of MGPC

Myristyl-gamma-picolinium chloride (miripirium chloride)

Myristyl-gamma-picolinium or miripirium chloride (MGPC) (Fig. 1) is a cationic germicidal substance used as a preservative in the single-dose formulation of the Depo-Medrol suspension (Table 4). The data on the miripirium chloride toxicity are very restricted in animal studies and in case reports [40–42]. Results are summarized in Table 5. First in 1946, Nelson et al. studied the acute and chronic toxicity of MGPC in animals [40]. The lethal dose 50% (LD50) of the treated animals was 200 mg/kg subcutaneously, 7.5 mg/kg intraperitoneally, 30 mg/kg intravenously, and 250 mg/kg orally. Fatal doses of MGPC by intravenous administration caused cyanosis and necrosis causing loss of the tail in rats. For the chronic toxicity experiments, MGPC toxicities were reported at the level of 0.25% of the diet with retard of growth, at the level of 0.10% solution with death between 16 and 27 days. MGPC given orally caused at 100 and 40 mg/kg the death of the rats before 21st day. To evaluate the skin irritation, Nelson et al. applied a saturated 3% solution of MGPC in the inner surface of rabbit's ear. Seventy-two hours after the first application, the ear was damaged by inflammation, edema, and scab formation. Loewenstein et al. examined the toxic effects of MGPC on the visual system of rabbits by intravitreal injection of MGPC [43]. When concentrated MGPC solution (double of the level of Depo-Medrol) was injected, a permanent reduction in retinal function was noted. The degree of retinal deterioration was directly related to the concentration of MGPC in the solution injected. To localize the site of MGPC induced functional damage in the rabbit retina, Zemel et al. injected intravitreally various concentrations of MGPC in the rabbit eye [41]. Animals were killed and enucleated at time intervals of 24 h, 72 h, 4, and 6 weeks after the intravitreal injection. All eyes

Table 5 MPGC toxicity in animal and human

References	Sample	Protocol	Toxicity
Nelson and Lyster [40]	Rat	Acute toxicity using 10 mg/ml and 30 mg/ml solutions	LD50: 30 mg/kg IV, 7.5 mg/kg IP, 200 mg/kg SC, 250 mg/kg orally
	Rat	Chronic toxicity (day 1 to day 6) MGPC 0.25, 0.10, 0.05, and 0.025% of the diet or drinking water MGPC 100, 40, 10, and 5 mg/kg by stomach tube	At level 0.25%: retard of growth At level 0.10%: death between 16 and 27 days At doses 100 and 40 mg/kg: death before 21 days
	Dog	Chronic toxicity (day 1 to day 90) MGPC 0, 5, 10, and 20 mg/kg orally	Normal variations on the microscopic examination of the tissues
	Rabbit	Chronic toxicity by application of a saturated 3% solution of MGPC in the inner surface of ear Chronic toxicity by dropping 0.5 ml of MGPC solution into the conjunctive	Inflammation, edema, scab formation Conjunctiva
Loewenstein et al. [43]	Rabbit	Intravitreal injection of 0.1 ml solution containing MGPC at 0.38, 0.76, and 1.52 mg/ml	Permanent reduction in retinal function after 1.52 mg/ml MGPC injection
Zemel et al. [41]	Rabbit	Intravitreal injection of 0.1 ml solution containing MGPC at 0.38, 0.76, and 1.52 mg/ml	Swollen retina with disarrayed nuclear and plexiform layers at 24 h (60% of retinal damage reveled by the electroretinogram) Widespread retinal damage, which expanded beyond the site of injection at 6 weeks
Mathias and Robertson [44]	Human	Retrobulbar injection of Depo-Medrol in two cases treated for iridocyclitis	Conjunctival inflammation and edema due to hypersensitivity to MGPC determined by positive intradermal test reactions
Farm and Erikssohn [42]	Human	Intra-articular injection of Depo-Medrol in a woman with rheumatoid arthritis	Eczema confirmed by positive reactions to MGPC 0.1 and 0.03% skin test

treated with MGPC solution were prepared for histological examination and glial fibrillary acidic protein (GFAP) immunoreactivity, and compared with control (sham) eyes. Histological retinal damages like swollen retina with disarrayed nuclear and plexiform layers were reported after intravitreal injection of MGPC. The sensitive marker for retinal damage GFAP was positive staining in Muller cells (glial cell), regardless of the degree of morphologic damage. Mathias et al. published two case reports of inflammation and edema after retrobulbar injection of Depo-Medrol [44]. Both of patients had delayed hypersensitivity to MGPC as determined by positive intradermal test reactions of the drug. Farm et al. also described a contact allergy to MGPC in a patient treated by intra-articular injections of Depo-Medrol [42]. The reading test at day 7 showed a strong positive reaction to MGPC at 0.1 and 0.03%, while all skin test controls were negative (Table 5).

Polyethylene glycol (PEG)

Polyethylene glycol (PEG) 3350, a non-ionic detergent and polymer of ethylene oxide, is added to the commercially available methylprednisolone acetate forms as an excipient to increase their solubility (Table 4) [45]. The PEG has been shown to create necrosis of neuronal tissues and demyelination of peripheral nerves [46–48]. Data are summarized in Table 6. Benzon et al. investigated the effects of an exposure to different concentrations of PEG (3–40%) on an in vitro rabbit sheathed-nerve preparation showing no change in conduction velocity at PEG level (3%) of commercial preparation [46]. Nelson synthesized the dangers of PEG from MPA therapy by intraspinal injection [47]. The author pointed the deleterious effects of PEG on neural tissue, as well as on muscle and the connective tissue. The authors do not recommended its injection anywhere near the neural tissue. More recently, Knezevic et al. studied cytotoxic effect of commercially available MPA with and without reduced preservatives on rat sensory neurons [45]. They identified a cytotoxic effect of commercial MPA formula on rat sensory neurons as shown by higher caspase-3 expression. The caspase-3 is functionally required for the normal execution of cell death by apoptosis [49].

Methylprednisolone acetate toxicity

MPA is practically insoluble in water and formed small densely particles in the commercial sterile aqueous suspension. A study performed by Okubadejo et al. aimed to compare the effects of direct intravascular injection of particulate (MPA) and non-particulate steroids (dexamethasone, prednisolone) on the spinal cord and CNS [50]. Magnetic resonance imaging revealed upper cervical cord and brain stem edema only after injection of MPA. Histological analysis confirmed ischemic damage and neuronal necrosis. Authors demonstrated that particulate MPA caused neurologic deficits. In a recent study, Rijsdjik et al. assessed the safety of IT reformulated MPA form on dog spinal tissue. Authors obtained a preservative free MPA formulation containing less than 0.025 mg/ml MGPC [38]. Repeated administration of this MPA formulation revealed an inflammatory response in the intrathecal space. A possible origin of the inflammatory reaction was the presence of MPA particles of which half were larger than 20 µm in diameter. The inflammation caused by particulate materials could be explained by an activation of cytokine release and cell adhesion factors leading to macrophage and neutrophil migration [51–53].

Discussion

The additives of the MPA formulations as PEG and miripirium chloride can be neurotoxic when injected intrathecally. Adverse reactions have been reported with this administration route such as arachnoiditis, bladder dysfunction, headache, meningitis. Therefore, the FDA had a stronger warning in the label of Depo-Medrol contraindications stated, "Depo-Medrol Sterile Aqueous Suspension is contraindicated for intrathecal administration. Reports of severe medical events

Table 6 Polyethylene glycol toxicity

Reference	Sample	Protocol	Toxicity
Benzon et al. [46]	Rabbit	Effect of 1 h exposure to concentrations (3–40%) of PEG on in vitro rabbit sheathed-nerve preparation	The 3 and 10% PEG had no impact of the conduction velocity Both 20 and 30% PEG slowed the conduction velocities 40% PEG abolished the conduction velocity PEG in concentration up to 40% does not cause neurolysis
Nelson [47]	Human	Review of dangers from PEG by intraspinal injection	Sterile meningitis, arachnoiditis, or pachymeningitidis
Knezevic et al. [45]	Rats	Exposition of commercially MPA with either preservatives or different concentrations of preservatives to rat dorsal root ganglia sensory neurons	Cytotoxic effect of MPA with preservatives shown by increased caspase-3 expression No difference between the control cells and cells treated with MPA with reduced concentrations of PEG

have been associated with this route of administration". In France, this statement is not indicated in the label of the same drug. To reduce the adverse effects of intrathecal MPA, Candido et al. proposed to decrease the concentration of excipients by inverting a vial before aspirating the contents into a syringe for subsequent injection [48]. The average amount removed 85% PEG without change the level of MPA or the pH of the solution. This method should be considered as an alternative in patients with repeated IT Depo-Medrol injections. In addition, Ridjsik et al. showed that the centrifugation at 14,000 rpm for 10 min reduced to 93% of MGPC in the MPA syringe [38]. Another alternative is the use of methylprednisolone sodium succinate form such as Solu-Medrol that is available in preservative free formulation (1.6 mg monobasic sodium phosphate anhydrous; and 17.4 mg dibasic sodium phosphate dried). In general, excipients are essential components of parenteral drugs to maintain active drug solubility or stability, assure antimicrobial safety, reduce potential pain and irritation upon injection, and control drug delivery [54]. If the pharmaceutical excipients are usually considered inert, some of these have been associated with specific toxicity issues and with allergic and anaphylaxis reactions (e.g., benzalkonium chloride, propylene glycol, sorbitol), coloring agents (tartrazine), benzoates (parabens), solvents [55–58]. As noted in this study, PEG, a solvent with antimicrobial properties used in a wide range of pharmaceutical drugs, have been associated with cardiovascular, hepatic, respiratory, and CNS toxicity [58, 59].

Conclusions

In conclusion, IT MPA therapy seems not to be fully safe due to reported adverse events. The use of other forms of therapy without excipients and particulate matter should be emphasized such as soluble methylprednisolone sodium succinate. If a patient experiences an adverse reaction to be due to IT corticoid therapy, it is important for practitioners to consider the presence of excipients as the potential cause of the problem.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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