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Mesna, an unusual agent causing hypersensitivity reactions during chemotherapy



Sodium 2-mercaptoethane sulfonate (mesna) is a detoxifying agent used to prevent hemorrhagic cystitis in patients receiving chemotherapy with either high-dose cyclophosphamide or ifosfamide. It has a reported half-life of 22 minutes, is quickly excreted by the kidneys after infusion, and accumulates in the bladder, where it detoxifies urotoxic breakdown products of cyclophosphamide and ifosfamide.¹ Despite multiple reported dosage regimens, mesna is usually administered before or concomitant with the first dose of cyclophosphamide or ifosfamide, followed by bolus doses.

Common adverse effects of mesna include nausea, constipation, and abdominal pain, but hypersensitivity reactions are uncommon. Reported hypersensitivity reactions to mesna include fixed drug eruption,² acute febrile reactions,³ urticaria with angioedema, and anaphylaxis.^{4,5} In all reported patients with an immediate reaction to mesna, it was decided to discontinue the medication and tolerate the increased risk of hemorrhagic cystitis with cyclophosphamide or ifosfamide.

Drug desensitization is a safe and an effective way to ensure provision of optimal therapy in individuals with immunoglobulin (Ig)E-mediated reactions to medications.⁶ Through various mechanisms, desensitization induces a temporary state of tolerance to the drug that lasts as long as plasma levels are maintained.⁶ No desensitization protocol has been reported for mesna, and maintaining the desensitized state is expected to be difficult because of its short half-life, using a dosing regimen based on intermittent infusions. We report the case of a patient with an immediate hypersensitivity reaction to mesna who underwent a successful desensitization.

The patient was a 12-year-old girl with osteosarcoma of the femur. During her third cycle of chemotherapy, she received etoposide, without any incidents, followed by a concomitant infusion of ifosfamide and mesna. Within 15 minutes of starting the administration of ifosfamide and mesna, she developed hives, facial angioedema, and generalized itching. The infusion was discontinued, and she received intravenous antihistamines with an adequate response; tryptase and interleukin-6 levels were not withdrawn at the time. Following her reaction, she was referred to the allergy clinic. Review of her clinical history revealed that she had previously received ifosfamide twice and mesna in bolus 8 times without any reactions. Skin prick tests were performed with ifosfamide at 10 mg/mL⁷ and mesna at 100 mg/mL.⁴ Intradermal reactions were performed using 1:100, 1:10, and 1:1 dilutions of both drugs.^{4,7} Skin prick tests were negative

for ifosfamide and mesna, whereas intradermal reactions to ifosfamide were negative, and a positive reaction was observed for mesna with a 1:10 dilution (10 mg/mL). Skin testing to mesna was negative in 3 controls using a 1:10 dilution. The 1:1 dilution was found to be irritant in all controls and was not used in the patient.

She was diagnosed with an IgE-mediated reaction to mesna, and discontinuation of the drug was recommended. Because the risk of hemorrhagic cystitis with ifosfamide was considered high by oncology, desensitization was attempted. In the next chemotherapy cycle, etoposide was administered routinely without complications, followed by a desensitization to mesna. Two hours before desensitization, she received methylprednisolone 1 mg/kg, to prevent nausea, and cetirizine 10 mg. Desensitization was performed using the 3-bag 12-step method with a total infusion time of 8.7 hours and a maximum infusion rate of 40 mL/hour, equivalent to 1 mg/m²/min (Table 1), and was tolerated without any breakthrough symptoms. Ifosfamide was administered after desensitization was completed. Because the patient required daily doses of ifosfamide for 5 continuous days, and to maintain stable plasma levels, a continuous infusion of mesna was started immediately after desensitization using the same dilution as in bag 3 (2.391 mg/mL) and the maximum infusion rate in the desensitization protocol (40 mL/h). The patient completed chemotherapy without any breakthrough symptoms during the 5 days on a continuous infusion of mesna and daily ifosfamide.

We describe a rare case of mesna causing an IgE-mediated reaction to chemotherapy, with positive skin testing, successfully managed with desensitization.

Although skin testing to mesna has not been validated, we attributed clinical significance to test results based on the occurrence of symptoms suggestive of an IgE-mediated reaction within 15 minutes of the infusion of ifosfamide/mesna, negative testing to ifosfamide, negative testing to mesna in controls, and the uneventful administration of ifosfamide following mesna desensitization.

When a patient has developed a hypersensitivity reaction to a medication, strict avoidance is generally the best and safer option; however, in patients with malignancies and hematological and chronic inflammatory diseases, opting for a second line agent may negatively impact their quality of life and life expectancy. Desensitization provides a safe and feasible option in such cases.⁸ In this case, after deciding to continue mesna by desensitization, the peculiar pharmacokinetics of the drug had to be considered while designing the protocol and postdesensitization care, because the administration regimen could impact the therapeutic and toxic effects of mesna. Because of its short half-life, intermittent infusion of mesna after desensitization would have exposed the patient to an allergic

Table 1Mesna Desensitization Protocol (Mesna 400 mg/m², Example for a 1.46 m² Patient)

Premedication to be administered 2 h before desensitization					
1. Cetirizine (0.3 mg/kg, PO) (maximum dosage 10 mg)					
2. Methylprednisolone (1 mg/kg, IV)					
Solution	Total volume (Saline, mL)	Drug per bag (mg)		Concentration (mg/mL)	
1	250	6.0		0.024	
2	250	60.0		0.240	
3	250	597.639		2.391	
Step	Solution	Rate (mL/h)	Time (min)	Dose per step (mg)	Cumulative dose (mg)
1	1	1	15	0.0060	0.0060
2	1	2.5	15	0.0150	0.0210
3	1	5	15	0.0300	0.0510
4	1	10	15	0.0600	0.1110
5	2	2.5	15	0.1500	0.2610
6	2	5	15	0.3000	0.5610
7	2	10	15	0.6000	1.1610
8	2	20	15	1.2000	2.3610
9	3	5	15	2.9882	5.3492
10	3	10	15	5.9764	11.3256
11	3	20	15	11.9528	23.2784
12	3	40	361.875	576.7216	600.000

Abbreviations: IV, intravenous; PO, by mouth.

NOTE. Total infusion time = 526.875 minutes.

reaction. Considering the risk of a reaction with intermittent dosing, we evaluated the use of a continuous infusion after desensitization. Before we selected this approach, a literature review reported that continuous infusion of mesna was more effective than intermittent dosing in preventing hemorrhagic cystitis in specific patients,⁹ and that continuous infusion of ifosfamide/mesna is a safe alternative to bolus administration in pediatric patients.¹⁰ To sustain plasma levels and prevent breakthrough reactions, and considering available safety and effectiveness data, we decided for a continuous infusion of mesna after desensitization, which allowed us to safely administer mesna to our patient, for 5 days.

Final infusion rates in this protocol are lower than those used for adults. This was done taking into consideration previous desensitization protocols tailored to children and that the traditional final infusion rate of 80 mL/h would have covered all the daily fluid requirements during the continuous infusion stage in our patient (1300 mL/m²).

This case illustrated the need to factor in the drug's pharmacokinetics while designing desensitization protocols and showed that continuous infusion could be considered as part of postdesensitization care for patients requiring drugs with short plasma half-life.

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