

# Nonimmediate allergic reactions induced by Mesna

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## Abstract

Mesna (2-mercaptoethane sulfonate Na), a drug that alleviates cyclophosphamide (CYC)-induced hemorrhagic cystitis, is frequently used to treat cancer and collagen diseases. A 33-year-old woman presented with high fever during CYC-based induction therapy for systemic lupus erythematosus. Her final diagnosis was mesna-induced drug hypersensitivity. Although mesna is widely used, allergic reactions are rare. This may be because of misdiagnosis as a primary disease flare-up, infection, or CYC-induced hypersensitivity reaction, which are commonly reported. Thus, accurate diagnosis is important for completion of the CYC-based regimen.

## KEYWORDS

cyclophosphamide, drug hypersensitivity, lupus erythematosus, mesna, systemic

## 1 | BACKGROUND

Cyclophosphamide (CYC) is a potent anticancer and immunosuppressive agent. Side effects, however, have become a problem. As a countermeasure against CYC-induced hemorrhagic cystitis, mesna (2-mercaptoethane sulfonate Na) is often used. We report on an adult case of mesna allergy during induction therapy for systemic lupus erythematosus (SLE). This is a rare pitfall that is difficult to diagnose.

## 2 | CASE REPORT

A 33-year-old woman was diagnosed her disease as SLE at our hospital 5 months ago. Her kidney biopsy results confirmed diffuse and membranous lupus nephritis (IV(A) + V). Mycophenolate mofetil (MMF) was off-label prescription drug for treating SLE before 2014; therefore, we administered prednisolone (pulse therapy with intravenous methylprednisolone 1000 mg/d for 3 days, followed by high-dose oral prednisone (PSL) 60 mg/d) and tacrolimus 3 mg/d to preserve fertility. After 4 months, she developed avascular necrosis (pre-collapse stage) of the right side of the femoral head. Concomitantly, her condition worsened (Table 1). We determined that the current induction therapy was unsuccessful.

Therefore, she was hospitalized for the second time for low-dose intravenous cyclophosphamide pulse therapy (IVCY, biweekly for 3 months). First, she underwent pulse therapy with intravenous methylprednisolone (500 mg/d for 3 days), followed by high-dose oral PSL (50 mg/d). After 10 days, 500 mg of intravenous CYC was administered (Figure 1). She was also administered intravenous mesna.<sup>1,2</sup>

Two weeks later, she received a second IVCY course. Subsequently, she demonstrated chills with high fever (39.0°C), lasting no more than 24 hours (Figure 1). She had no rash or symptoms of upper respiratory or urinary tract infections. Her blood and imaging test results were normal; no leukopenia was found (WBC, 3950/μL; Lym 22.9%).

Upon the third IVCY course (Figure 1), she had another high fever episode (40.1°C), which rapidly subsided without medication (leukocyte, 5140/μL; Lym, 18.7%). We presumed the fever was related to the IVCY because of the defervescence in a short period, bradycardia, and lack of other signs. She also explained that her body suddenly became hot during the mesna drip. The possible causes of the drug allergy were CYC and mesna; however, determining the real cause is difficult. We explained that we were unable to determine the cause, and that an alternative drug (MMF) was off-label prescription drug. After obtaining patient consent, we proceeded with a fourth IVCY course without mesna. During this course (Figure 1), she had no chills or fever until after 2 weeks. Therefore, we regarded this case as mesna

**TABLE 1** Laboratory data on admission

CBC			LDH	185	IU/L	Immunological examination		
WBC	6140	/ $\mu$ L	CPK	40	IU/L	ANA	>1280 (SPECKLED)	
Neut	86.4	%	T.Chol	147	mg/dl	Anti-dS-DNA IgG	356	IU/ml
Eos	0.3	%	TG	183	mg/dl	Anti-SS-A	>500 U/ml	
Baso	0.2	%	BUN	17.3	mg/dl	C3	48	mg/dl
Lymph	10.7	%	Cr	0.76	mg/dl	C4	11	mg/dl
Mono	2.4	%	UA	7.8	mg/dl	CH50	<12.0 U/ml	
Hb	12.0	g/dl	Na	139	mEq/l	Urinalysis		
Plt	22.5	$10^4/\mu$ L	K	4.8	mEq/l	PH	6.0	
			Cl	108	mEq/l	Protein	(2+)	
Biochemistry			Ca	8.9	mg/dl	Occult blood	(3+)	
TP	5.8	g/dl	P	4.7	mg/dl	RBC	10-19	/HPF
Alb	3.0	g/dl	CRP	0.03	mg/dl	WBC	30-49	/HPF
T-Bil	0.21	mg/dl	BS	104	mg/dl	hyaline cast	11-30	/WF
ALP	196	IU/L	HbA1C	6.0	%	granular cast	1-10	/WF
r-GTP	33	IU/L				white cell cast	1-10	/WF
AST	22	IU/L				urine protein	1.4	g/gCr
ALT	23	IU/L						

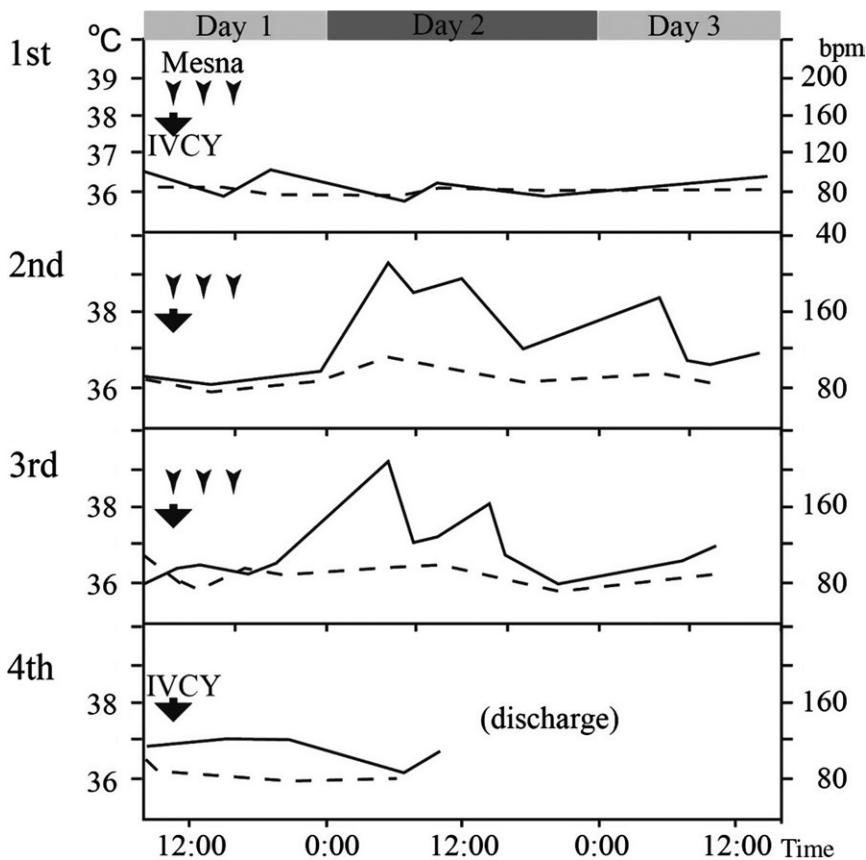
HPF, high power field; WF, whole field.

hypersensitivity. IVCY was administered without mesna until the sixth course. Thereafter, no fever occurred.

Subsequently, she underwent maintenance therapy with azathioprine (2 mg/kg) and prednisolone. She achieved remission after 6 months and remained symptom-free without any relapse.

### 3 | DISCUSSION

We encountered a case of mesna allergy during the second and third course of CYC-based induction therapy for SLE. After discontinuing



**FIGURE 1** Body temperature (continuous line) and heart rate (dashed line) chart during the first fourth cycles in sixth of induction therapy. CYC (arrow. 500 mg at 10:00 o'clock) and mesna (arrow head. 160 mg each at 9:30, 13:00, 17:00 o'clock)

mesna, the treatment course concluded uneventfully. This case represents a rare documentation of mesna-induced hypersensitivity in SLE treatment.

Mechanisms of drug-related fever are multifactorial, which include hypersensitivity reactions, altered thermoregulatory mechanisms, reactions directly related to administration, drug pharmacologic action extensions, and idiosyncratic reactions. However, hypersensitivity is the most frequent factor as a result of type I and IV hypersensitivity responses. A type IV delayed hypersensitivity reaction can be mistaken as relapse or infection. Fever during SLE is almost always caused by an infection or flare-up of the disease. Thus, determining the frequency of drug allergy is difficult. Further, SLE often causes drug-related fever.<sup>3,4</sup> Sulfa agents and NSAIDs commonly cause fevers, as well as immunosuppressive agents, such as CYC.<sup>5</sup> However, these events are often unpredictable.<sup>6,7</sup>

Cyclophosphamide remains a central anticancer and immunosuppressive agent. However, it has many side effects, including bone marrow suppression, infertility, bladder cancer, and hemorrhagic cystitis. Thus, managing these side effects is important. As direct stimulation of a CYC metabolite causes bladder problems, adequate hydration is necessary to reduce bladder toxicity. However, with nephrotic syndrome and heart failure, which are often observed in SLE patients, mass replacement fluid therapy is difficult. Thereby, mesna is frequently used as a drug to reduce bladder toxicity. Compared to oral CYC, IVCY is a low-risk treatment,<sup>8</sup> but mesna has been weakly recommended.<sup>1</sup>

Compared to CYC, reports of mesna allergy are scarce,<sup>9</sup> because it can be difficult to diagnose. As described above, drug-related fever may not be suspected as quickly as infection and relapse. Additionally, drug-related fever may, in some cases, be unwittingly improved by discontinuation or change in an immunosuppressive agent. Further, although drug-related allergy is determined during CYC and mesna usage, making a definite diagnosis is difficult owing to a need for a challenge test in most cases. Diagnosis through the utilization of a CYC or its metabolites and an intradermal test has been reported, but its diagnostic accuracy is low.<sup>10</sup> Even in our case, we could not do a challenge test as describe above. Thus, we diagnosed the allergy from circumstantial evidence.

## 4 | CONCLUSIONS

In conclusion, promptly identifying mesna-induced hypersensitivity is difficult. Although mesna allergies appear to be rare, proper diagnosis can facilitate completion of treatment with CYC. CYC is still an important agent for treating severe collagen diseases. Further, alternative drugs are few. Thus, mesna hypersensitivity is an essential condition to remember during CYC treatments.

## ACKNOWLEDGEMENTS

None.

## CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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**How to cite this article:** Shimogori K, Araki M, Shibazaki S, Tuda K, Miura K. Nonimmediate allergic reactions induced by Mesna. *J Gen Fam Med*. 2017;18:285–287. <https://doi.org/10.1002/jgf2.79>