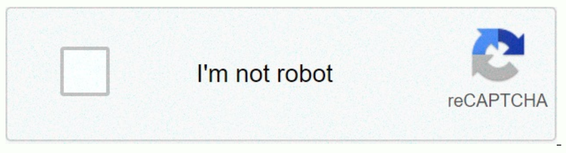

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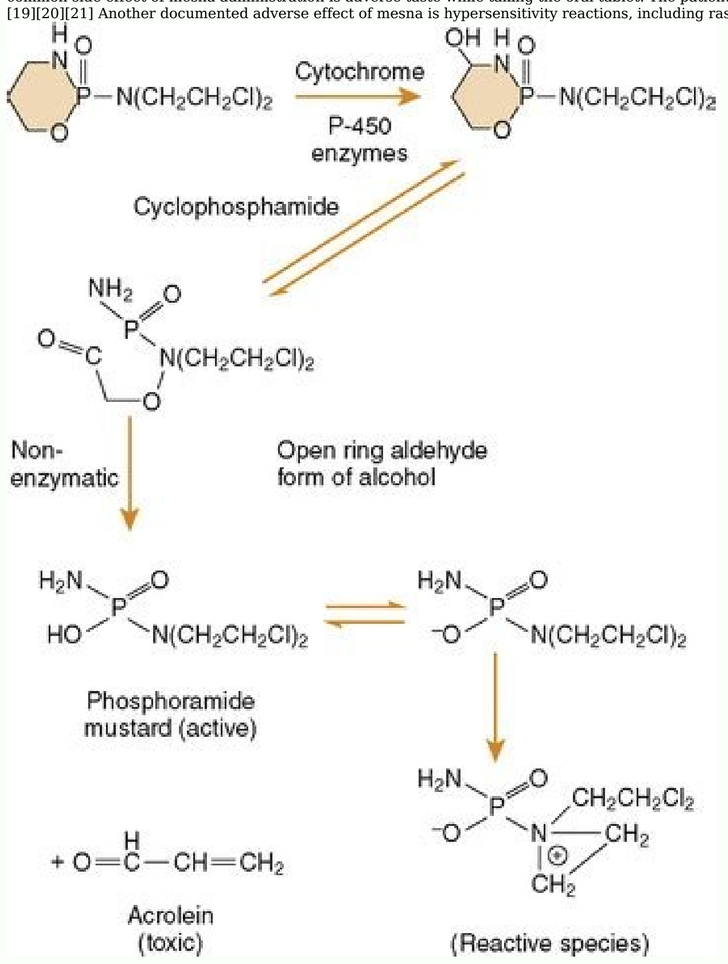
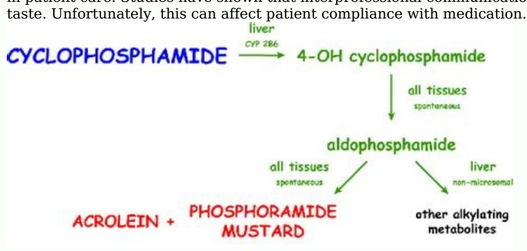
Mesna mechanism of action pdf

Mesna mechanism. Mechanism of action of mesna. Mesna chemical structure.

Mesna (sodium 2-mercaptoethane sulfonate) is a detoxifying medicine used to prevent hemorrhagic cystitis in patients receiving chemotherapy with either high-dose cyclophosphamide or ifosfamide. Mesna initially becomes inactivated to dimesna (mensa disulfide) in the bloodstream; however, once it is filtered through the kidneys and excreted into the bladder, it is reactivated. As reactivated mesna concentrates in the bladder, mesna detoxifies acrolein, a urotoxic breakdown product of ifosfamide and cyclophosphamide that accumulates in the bladder. This activity outlines the indications, action, and contraindications for mesna as a valuable agent in conjunction with the ifosfamide or cyclophosphamide administration. In addition, this activity will highlight the mechanism of action, adverse event profile, and other vital factors pertinent for interprofessional team members in the care of patients receiving chemotherapy at risk for hemorrhagic cystitis. Objectives: Describe the mechanism of action of mesna in preventing hemorrhagic cystitis. Summarize the adverse effects associated with mesna administration. Outline various forms of administration of mesna. Review interprofessional team strategies for improving care coordination and communication to advance mesna and improve outcomes. FDA-approved Indication Mesna is a prophylactic medication to reduce the incidence of ifosfamide-induced hemorrhagic cystitis.[1] It is important to recognize that mesna is not indicated to decrease the risk of hematuria due to thrombocytopenia. Non-FDA-approved Indications Mesna is also used widely as a prophylactic medicine to reduce the incidence of cyclophosphamide-induced hemorrhagic cystitis. Treatment of chemically-assisted dissection of recurrent and residual cholesteatoma[2] Reduction of the incidence of BK viruria following post-transplantation cyclophosphamide[3] Inhibition of propylene glycol-induced cholesteatoma formation[4] Treatment of pain following failed back surgery syndrome via epidural injection[5] Treatment of chronic cholesteatomatous otitis media in children[6] Mesna (sodium 2-mercaptoethane sulfonate) is a detoxifying agent used to prevent hemorrhagic cystitis in patients receiving chemotherapy with either high-dose cyclophosphamide or ifosfamide. Mesna initially becomes inactivated to dimesna (mensa disulfide) in the bloodstream; however, once it is filtered through the kidneys and excreted into the bladder, it is reactivated. As reactivated mesna concentrates in the bladder, mesna detoxifies acrolein, a urotoxic breakdown product of ifosfamide and cyclophosphamide that accumulates in the bladder. Acrolein stimulates the release of inflammatory mediators interleukin-1 beta, TNF-alpha, and endogenous nitric oxide inducing vascular dilatation, mucosal edema, and capillary fragility resulting in hemorrhagic cystitis.[7] Mesna acts as a sulfhydryl donor that forms a conjugate bond with acrolein and inactivates it, preventing hemorrhagic cystitis or bleeding due to bladder irritation.[8]There is some evidence to suggest that this might also occur through the inhibition of lactoperoxidase (LPO). Lactoperoxidase utilizes hydrogen peroxide (HO) and thiocyanate (SCN) to produce hypothiocyanous acid (HOSCN). Mesna's sulfhydryl group binds stably to LPO within the SCN binding site and thus inhibits function resulting in the reduction and regulation of local inflammatory effects.
[9]PharmacokineticsAbsorption: After oral administration, peak plasma concentrations are attained within 1.5 to 4 hours for free mesna and 3 to 7 hours for total mesna (mesna plus dimesna and mixed disulfides). Food does not alter the bioavailability of orally administered mesna.Distribution: Mean apparent volume of distribution (aVd) for mesna is 0.65 ± 0.24 L/kg following IV administration, suggesting distribution to total body water. A fraction of mesna is bound to albumin in plasma. Metabolism: Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna), and mixed disulfides. Mixed disulfides have been postulated to play an important role in nephroprotection through inhibiting enzymes γ-glutamyltranspeptidase (GGT) and aminopeptidase N (APN).[10]Excretion: After IV administration of mesna 800 mg, approximately 32% and 33% of the administered dose are excreted in the urine as mesna and dimesna, respectively. Mesna is available in 100 mg/ml injection, which can be administered as an IV infusion. It is also available as a 400 mg oral tablet.Mesna is usually administered as an injection concurrently with cyclophosphamide or ifosfamide chemotherapy.
If the physician deems it is still necessary after the initial dosage, an oral form (400 mg tablet) is usually administered 2 to 6 hours following subsequent therapy. Due to the strong adverse taste of oral mesna tablets, administering the tablet with juice or food is usually the recommendation due to the sulfur odor/taste.
Patients are advised to drink at least 4 cups of liquid daily while taking mesna.[11]Dilute the volume of mesna injection in 5% dextrose injection, 5% dextrose, 0.45% sodium chloride injection, 0.9% sodium chloride injection, or lactated Ringer's Injection to obtain a final concentration of 20 mg/mL.American society of clinical oncology (ASCO) guidelines recommend following protocols for administering mesna.[12]Mesna dosing recommendations with standard-dose ifosfamide: ASCO recommends that the daily dose of mesna be calculated to be equivalent to 60% of the total daily dose of ifosfamide, given as three bolus doses given 15 minutes before and four and eight hours after administration of each dose of ifosfamide when the ifosfamide dose is less than 2.5 g/m/day administered as a short infusion. When mesna is used with continuous ifosfamide infusion, it may be given as a bolus dose equivalent to 20% of the total ifosfamide dose, followed by a constant infusion of mesna equivalent to 40% of the ifosfamide dose, given for 12 to 24 hours after completion of the ifosfamide infusion.Mesna dosing recommendations with high-dose ifosfamide: The efficacy of mesna for the prevention of urotoxicity with very high-dose ifosfamide (>2.5 g/m/day) has not been established. The half-life of ifosfamide is extended at higher doses. Consequently, prolonged mesna dosage regimens may be required for protection against urotoxicity. A higher concentration of ifosfamide (50 mg/mL) is incompatible with mesna and can decrease the stability of ifosfamide.Mesna dosing recommendations by the oral route: ASCO recommends administering mesna as an IV bolus injection in a dose of 20% of the ifosfamide dose at the time of ifosfamide administration; mesna tablets are administered orally in a dosage equal to 40% of the ifosfamide dose at 2 and 6 hours following each dose of ifosfamide; the total daily dose of mesna is 100% of the ifosfamide dose; patients who vomit within 2 hours of taking oral mesna should repeat the dose or receive IV mesna; the dosing schedule should be repeated on each day that ifosfamide is administered.Mesna recommendations with cyclophosphamide: Mesna plus saline diuresis or forced saline diuresis is advised to reduce the incidence of urotoxicity associated with high-dose cyclophosphamide. It is important to note that mesna injection should not be mixed with cyclophosphamide, cisplatin, carboplatin, and epirubicin. According to KDIGO (kidney disease improving global outcomes) guidelines, mesna should be administered if the cyclophosphamide dosage is considered high.[13]Studies have also shown mesna administration as a topical agent for chemically assisted dissection of recurrent and residual cholesteatoma, most commonly in pediatric patients.[14] Another study showed that epidural injection of mesna reduced pain following failed back surgery syndrome (FBSS).[5] Use in Specific Patient PopulationsPatients with Hepatic Impairment: No clinical studies have been performed to assess the effect of hepatic impairment.Patients with Renal Impairment: No clinical studies have been performed to assess the effect of renal impairment.Pregnancy Considerations: As per the manufacturer's labeling information, it is considered the former FDA pregnancy category B medicine. Clinicians should also inform the risk associated with ifosfamide/cyclophosphamide therapy. According to ACOG, in addition to pretreatment fertility conservation counseling, sexually active young women should be informed about the risks of becoming pregnant during cancer treatment. Clinicians should also guide, and women should also receive counseling regarding effective contraception.[15]Breastfeeding Considerations: An essential consideration of mesna administration is the breastfeeding status of females of reproductive age.[16] It is not well understood if mesna is present in breast milk; however, benzyl alcohol is often a component of mesna intravenous formulations. The manufacturer indicated that exposure to the breastfeeding infant is unlikely in part due to maternal metabolism. Nonetheless, benzyl alcohol has been linked to adverse events in infants, and therefore breastfeeding is not recommended for at least one week after the last mesna injection.[17] Mesna in oral and IV administrations is commonly associated with gastrointestinal side effects, including nausea, vomiting, constipation, abdominal pain, and bad taste.[18] The most common side effect of mesna administration is adverse taste while taking the oral tablet. The patient can often vomit due to the unpalatable taste, and it is a strong recommendation to take mesna along with a strong-tasting liquid. Dermatologic reactions range from fixed drug eruptions to photo-distributed dermatosis and steven johnson syndrome.[19][20][21] Another documented adverse effect of mesna is hypersensitivity reactions, including rash and leukopenia.



Systemic anaphylaxis has also been reported.[22][23]Laboratory Test - Interactions No clinical drug-drug interaction studies have been conducted with mesna in clinical trials. False-negative CPK levels may be reported due to interference with enzymatic creatinine phosphokinase (CPK) activity tests that utilize a thiol compound for CPK reactivation. A false-positive reaction for ascorbic acid can be observed in the presence of mesna (Tillman's reagent-based urine screening tests).[24] False positive tests for urinary ketones may occur in patients who are given mesna when using nitroprusside sodium-based urine tests (dipstick tests).[25] Mesna prophylaxis is contraindicated in patients with hypersensitivity to thiol compounds and those who previously had adverse reactions associated with a prior mesna administration.[26] Mesna prophylaxis is also contraindicated in patients with hypersensitivity or prior adverse reactions to benzyl alcohol (an excipient used in mesna).[17][27] Along with mesna administration, providers must monitor urine for signs of hematuria and monitor urine output and hydration status. Few patients often have breakthrough hematuria, even if they are on mesna prophylaxis. If the physician deems mesna administration subtherapeutic as hemorrhagic cystitis is still present, an additional IV bolus or oral tablet may be administered. Finally, it is essential to monitor patients for signs/symptoms of hypersensitivity or dermatologic toxicity. Reactions associated with mesna are rare; however, mesna has the potential to lead to severe hypersensitivity reactions, including anaphylactic shock.[20]Perform pregnancy tests for women of reproductive potential before initiating the medicine, as it is often used with other chemotherapeutic treatments.[15] There is no indicated antidote to mesna overdose. Mesna administration is usually via IV bolus or an oral tablet, and therefore, unlike a drip, it cannot be immediately stopped with the appearance of adverse effects. If a hypersensitivity reaction is present after administration, supportive care with fluid administration is recommended.[23] Consultation with a medical toxicologist or poison control center is useful in complex cases. Managing adverse reactions associated with any drug administration requires an interprofessional team of healthcare professionals, including a nurse, laboratory technologists, pharmacists, and several clinicians involved in patient care. Studies have shown that interprofessional communication in the healthcare environment significantly improves patient outcomes and healthcare cost burden regarding repeat imaging, labs, and advanced testing.[28][29][30] [Level 2, Level 3]The most common adverse effect of mesna administration, particularly oral, is bad taste. Unfortunately, this can affect patient compliance with medication.



In addition, if patients do not adhere to the regimen, it may lead to urinary tract irritation and hemorrhagic cystitis associated with ifosfamide and cyclophosphamide. To avoid this, healthcare providers at every level must effectively communicate the importance of taking this drug and discuss strategies to help make it more palatable. Examples of such measures include administering the medication with a strong-tasting liquid such as grape juice or crushing up the oral drug and mixing it into more palatable foods such as apple sauce.However, beyond the taste of mesna, there are additional adverse effects that one cannot afford to miss. Without proper management and monitoring, these can lead to more dire consequences, such as hypersensitivity reactions. As mesna is not a drug that is commonly associated with these serious adverse effects, healthcare providers are prone to take these reactions for granted or not consider mesna as the culprit. As soon as the patient presents with any adverse reaction to the nursing staff, they must promptly notify a physician.Once notified, it is also imperative that clinicians communicate with urologists for hemorrhagic cystitis and immunologist for hypersensitivity reactions. Anaphylaxis requires coordination between emergency department physicians and critical care physicians. In overdose, consultation with a medical toxicologist is crucial. Pharmacists should verify the dosing and schedule of mesna and ifosfamide. Numerous case series have been associated with the adverse effects of mesna usage.[21][23][22] Therefore, collaboration and coordination between the interprofessional team consisting of clinicians (MD, DO, NP, PA), specialists, nursing staff, and pharmacists are crucial to improving patient outcomes related to mesna therapy. [Level 5] Mesna (sodium 2-mercaptoethane sulfonate) is a detoxifying medicine used to prevent hemorrhagic cystitis in patients receiving chemotherapy with either high-dose cyclophosphamide or ifosfamide. Mesna initially becomes inactivated to dimesna (mensa disulfide) in the bloodstream; however, once it is filtered through the kidneys and excreted into the bladder, it is reactivated. As reactivated mesna concentrates in the bladder, mesna detoxifies acrolein, a urotoxic breakdown product of ifosfamide and cyclophosphamide that accumulates in the bladder. This activity outlines the indications, action, and contraindications for mesna as a valuable agent in conjunction with the ifosfamide or cyclophosphamide administration. In addition, this activity will highlight the mechanism of action, adverse event profile, and other vital factors pertinent for interprofessional team members in the care of patients receiving chemotherapy at risk for hemorrhagic cystitis.