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Experimental study: a comparison of the uro -protective efficacy of mesna with hyperhydration in cyclophosphamide-induced haemorrhagic cystitis in sprague dawley rats

Abstract

Background: Haemorrhagic Cystitis (H.C) is well known as a dose-limiting side effect of cyclophosphamide (CyP).

The aim of this study was to investigate the effect of Mesna in protecting against CyP-induced H.C and compare its efficacy to that of hyperhydration.

Research design: This animal study was conducted at the Hospital Clinic de Barcelona's Experimental Animals Breeding and Medical Research Centre.

Materials and Methodology: Male Sprague Dawley rats (360-510 g, 5 rats per group) were divided into four groups at random: No medications were given to Group 1 (Control group). Group 11 (received CyP 150mg/kg intraperitoneally alone), Group 111 (received CyP150mg/kg, and mesna 150 percent of the CyP dose immediately and at 4 and 8 hours after administration of CyP, both drugs IV injection by intra jugular vein), and Group 1V (received CyP150mg/kg, and hyperhydration by catheterization of the animal jugular vein with a constant infusion of glucose water 5%, 3ml/hour/48 hours).

48 hours later, the bladders of the animals were examined macroscopically and histologically. The existence of edema and haemorrhagic edema, as well as histological and gross evaluations of bladder injury, were assessed, and statistical analysis was employed.

Results: HC was found in all of the animals in group 11. When compared to group 1 (p0.001), this group had significantly more histological damage and macroscopic alterations.

When compared to group 11, the median ratings of bladder injury in groups 111 and 1V were considerably lower. There was significant difference between groups 11 apart, and both groups111, 1V when the median scores for bladder injury were compared.

Conclusion: This study shows the efficacy of mesna or hyperhydration in the prevention of cyclophosphamide-induced haemorrhagic cystitis.

Keywords: mesna, cyclophosphamide, haemorrhagic cystitis, hyperhydration

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Yasin Idweini, B Umbert, M Sole, Pablo Carretero

Urology Department, Histopathology Department-Hospital Clinic de Barcelona -University of Barcelona, Spain

Correspondence: Yasin Idweini, Urology Department, Histopathology Department-Hospital Clinic de Barcelona -University of Barcelona. C/Villarroel,170. 08036 Barcelona, Span, Email yasin_idweini@hotmail.com

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Introduction

Since the beginning of allogeneic hematopoietic cell transplantation, haemorrhagic cystitis (HC) has been recognized as a serious complication. The bladder mucosa is immediately damaged by high-dose chemotherapy used in conditioning regimens, such as cyclophosphamide and busulfan, or their combination, resulting in early HC.[1,2]

Cyclophosphamide (CyP) is an alkylating chemotherapeutic drug used to treat cancers such as lymphoma, ovarian cancer, and breast cancer.

Haemorrhagic cystitis is a well-known and major life-threatening adverse effect of this drug.[3]

CyP is a prodrug that the P-450 enzymes in the liver convert into the active metabolites phosphoramide mustard and acrolein. Acrolein has been shown to be a powerful urothelial irritant and is now recognized as a primary contributor to cyclophosphamide-induced HC. Urothelial injury is thought to be caused by direct contact with acrolein, which results in edema, ulceration, neovascularization, haemorrhage, and necrosis.[4]

In clinical practice, adequate hydration and the concomitant injection of sodium-2-mercaptoethane (mesna) are the most often used treatments for preventing CyP-induced HC. Haemorrhagic cystitis in some studies however, occurs in 10-40% of mesna-treated patients.[5]

Materials and methodology

A total of 20 male Sprague Dawley rats were randomly divided to four groups of five rats each, with free access to food and water. Five male Sprague Dawley rats (about 360-510 g) were used in each group. No medicines were given to Group 1 (the control group). Group 11: (got CyP 150mg/kg intraperitoneally as a single dose). Group 111: (got CyP 150mg/kg and mesna 150 percent of the CyP dosage in three doses: immediately, 4 hours later, and 8 hours later, both medications intravenous injection through intra jugular catheterization). Group 1V: (got 150mg/kg of CyP intravenous injection and hyperhydration

through intra-jugular vein infusion of glucose water at 5%, 3ml/hour for 48 hours).

After receiving CyP, the animals were slaughtered 48 hours later. Their bladders, ureters, and kidneys were surgically removed and preserved in 10% formalin before being submitted for histological analysis.

Animals' diuresis haematuria and bladders were examined macroscopically and histologically. The presence of edema and haemorrhage, as well as histological examination of bladder injury, were graded, and statistical analysis was employed.

Results

The weights of all the animals were nearly equal. There is significant difference between groups 11 and 111 in terms of diuresis and haematuria, however there is a significant difference between groups 11 and 1V (p= 0.0169) and 111. Both approaches mesna (p=4.512E-03) and hyperhydration group (p=0.0301) showed high effectiveness in histopathological lesions. The Mesna group outperformed the hyperhydration group by a factor of (p=0.0301).

In terms of preventing vesical edema, the Mesna group outperforms the hyperhydration group (p = 0.o379).

Discussion

In this study, we compared the effectiveness of mesna and hyperhydration in the prevention of CyP-induced HC in this research. CyP usage has been linked to mutagenesis and bladder cancer, particularly in people who have acquired cystitis.[6,7] Haemorrhagic cystitis is a syndrome linked to a number of diseases as well as medication, virus, and toxin exposure. It shows up as widespread bleeding of the bladder's endothelial lining. Bladder mucosa damage is because of acrolein, a metabolite of cyclophosphamide, which has direct toxic effect on urothelium .Mesna is considered prophylaxis treatment in high dose Cyclophosphamide this drug combines with acrolein and detoxifies the drug reducing bladder toxicity(8) .On cystoscopy urologists found diffuse hyperaemia ecchymosis and petechiae which bleeds actively and it treats with plenty of oral fluids, bladder irrigation thus reducing the time of contact with acrolein with bladder mucosa thereby minimising the chance of cystitis

According to these findings, mesna and hyperhydration are equally beneficial in avoiding CyP-induced haemorrhagic cystitis in bone marrow transplant patients.[8,9]

Conclusion

This study shows that mesna is more effective than hyperhydration in avoiding CyP-induced haemorrhagic cystitis; however, hyperhydration is not as effective as mesna in preventing HC.

Acknowledgments

None.

Conflicts of interest

The author declares there is no conflict of interest.

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