Letter to the Editor

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The addition of MESNA in vitro prolongs prothrombin time similar to N-acetyl cysteine

Keywords: coagulation; sodium 2-sulfanylethanesulfonate (MESNA); thromboelastometry.

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To the Editor,

As has been previously reported, N-acetyl cysteine (NAC) prolongs the prothrombin time (PT) ratio in healthy subjects in studies in vitro and in vivo. Interfering with the sulfhydryl groups, NAC may depress the activity of coagulation factors II, VII and X [1–3]. We investigate if sodium 2-sulfanylethanesulfonate (MESNA), an antioxidant used intravenously to protect the bladder from the effects of the chemotherapy drug cyclophosphamide [4], which shares molecular structure with NAC, exerts a similar effect on coagulation. Moreover, little is known about the effect of MESNA on global hemostatic tests as thromboelastometry (TEM). We study the in vitro effect of MESNA in 11 healthy volunteers, by standard coagulation tests and TEM (ROTEM, Tem International GmbH, Germany). Samples of whole blood were incubated with saline (baseline) or 1000 μM or 2000 μM of MESNA at 37°C for 1 h. We used a concentration of 1000 μM of MESNA, because this is comparable to the levels reached in vivo during the first hours of infusion [5]. The assay was also performed with 2000 μM of MESNA, to detect any possible dose-dependent effect. PT ratio and activated partial thromboplastin time (aPTT) were measured. EXTEM tests were performed by ROTEM, and the following parameters were evaluated: clot time (CT), clot formation time (CFT), α angle, maximum clot firmness (MCF), and clot lysis at 60 min [6].

All baseline values were within the normal range. After the addition of 1000 μM of MESNA, PT ratio increased significantly: from 1.06±0.08 to 1.19±0.10 (p<0.01) (normal range 0.85–1.10), whereas no significant changes were seen in the aPTT values. In the EXTEM test (Figure 1), CT, CFT, and α angle remained unchanged. MCF decreased from 63±3 mm to 62±3 mm (p<0.01). No significant changes were observed in clot lysis parameters. After adding 2000 μM of MESNA, there was a significant prolongation of PT ratio as regards baseline values. However, the values did not significantly differ in comparison to those observed with 1000 μM of MESNA. aPTT values remained unchanged. It is of note that no changes were observed after 2000 μM of NAC in the EXTEM parameters versus baseline values.

In patients treated with cyclophosphamide, hemorrhagic cystitis can develop with variable incidence, whereas microhematuria is seen in 93% [7]. “Acrolein, a toxic derivate from cyclophosphamide, damages epithelial urinary bladder being the suspected mechanism; however this symptom, could raises doubts about coagulation competence in this population”. In this study, the addition of MESNA produced a significant increase in the PT ratio without any changes in aPTT; no effects were observed in the EXTEM assays, except for a slight decrease of the MCF, so small that it does not allow for any interpretation values. The routine coagulation tests did not correlate with the findings in the EXTEM tests: the CT reflects the latency of activation of the coagulation cascade, so that CT has been associated with PT ratio. CT, unlike PT ratio, was not affected by adding MESNA. A discrepancy between the routine coagulation laboratory tests and the TEM assay has been reported in several settings, as in acute liver failure or after liver resection, and might be attributed to differences in the studied sample (plasma vs. whole blood) and the endpoint measured (5% of fibrin clot vs. dynamic clot formation) [8, 9]. Moreover, TEM allows a coagulation assessment from a more functional point of view than the standard coagulation test and, consequently, nearest to
the clinical situation. In previous series from cardiovascular surgery, NAC prolonged the CT [10]. We did not see this effect with MESNA but the clinical context and the use of heparin can account for this discrepancy.

In conclusion, the addition of MESNA in vitro, similar to NAC, increases the PT ratio. These results were not consistent with those from TEM assay, which is assumed to assess the overall coagulation function, where MESNA did not produce any effect. These findings should be considered when evaluating coagulation tests in patients receiving MESNA.

Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Received May 8, 2013; accepted July 12, 2013; previously published online August 9, 2013

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