

**ISCHEMIA MODIFIED ALBUMIN AND THE EFFECT OF BOSENTAN IN ACUTE MESENTERIC ISCHEMIA**

It was with great enthusiasm, we read an article by Gulpinar et al., who recently reported the effect of bosentan on plasma ischemia modified albumin (IMA) levels in acute mesenteric ischemia. Their preliminary study results concluded that bosentan showed a protective effect on mesenteric ischemia and in lowering IMA levels.<sup>1</sup> However, based on our previous knowledge<sup>2,3</sup> and others,<sup>4-19</sup> this article by Gulpinar et al.,<sup>1</sup> generated great interest in addressing the following points.

Firstly, although IMA provides cost effective and less time consuming diagnostic variable for mesenteric ischemia, despite of its great sensitivity, there is strong evidence on its least specificity in detecting particular ischemic conditions. There are studies showing elevated levels of IMA in wide range of ischemic conditions.<sup>4-6</sup> Furthermore, IMA levels are also affected by various physiologic changes that cause oxidative stress, such as pregnancy, malignancy, chronic liver failure, end-stage renal failure, and thyroid disorders.<sup>2-12</sup> It is noteworthy that IMA has been proposed as an irrelevant marker in the early diagnosis of mesenteric ischemia.<sup>13</sup> In one study on rat model of mesenteric ischemia, although there is a direct correlation of histopathological evidence with ischemic damage and time, there is no significant increase in IMA levels.<sup>14</sup> In this animal model study IMA has been proposed to be not a reliable early marker of intestinal ischemia. But these studies were surprisingly not cited in the paper by Gulpinar et al.<sup>1</sup>

Secondly, IMA has been recently documented as a marker of oxidative stress. Therefore, generation of free radicals may result in excess formation of IMA. There is also evidence that different anaesthesia techniques may have different effects on the oxidative stress. A significant increase in IMA levels has been reported under general anaesthesia.<sup>15</sup> Moreover, under surgical conditions IMA increases with systemic oxidative stress and is more sensitive than these other parameters as an early marker of oxidative stress, and that levels increase before

ischaemic injury or reperfusion damage occur.<sup>15,16</sup> In support of this, IMA has been found to be correlated positively with malondialdehyde and interleukin-6 in mesenteric ischemia of rat model.<sup>17,18</sup> Therefore, it is clear that, general anaesthesia and laparotomy in this study could have influenced the results obtained.

Thirdly, it is more important to state here that albumin levels influence the IMA value.<sup>19</sup> Albumin concentrations may decrease due to surgical blood loss and fluid administration (laparotomy and administration of 3 ml/kg/hour saline in the study by Gulpinar et al).<sup>15</sup> Therefore, it is probable that this issue would have affected the high IMA values. Furthermore, this appears to be important as the group 1 in the study by Gulpinar et al had the mean IMA value of 0.509 absorbance units (ABSU) which is higher than that of the reference IMA value; over 0.400 ABSU as proposed by Bar-or et al to be abnormal.<sup>1,20</sup>

Finally, in addition to the endothelin receptor antagonistic role, bosentan has been recently showed to inhibit oxidative and nitrosative stress in occlusive pulmonary hypertension.<sup>21</sup> Considering this recent evidence into account, it appears that administration of bosentan could have resulted in improving oxidative stress and endothelial damage, lowering IMA levels. Despite the aforementioned information, it is of much importance that Gulpinar et al demonstrated IMA levels in the rat model of mesenteric ischemia and the effect of bosentan on IMA level.<sup>1</sup> We believe that the issues described here would provide much insightful concepts in discussing the significance of IMA in future studies.

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### AUTHORS' RESPONSE

It was of great pleasure to read the commentary article by Reddy et al. discussing our study titled "the effect of bosentan on plasma ischemia-modified albumin (IMA) levels in acute mesenteric ischemia".

In the search of a reliable marker for early detection of mesenteric ischemia; IMA levels are of interest and studied in many papers. Some of them indicating to be a valuable marker whereas some of the studies found the levels to be a non-reliable early marker.<sup>1-4</sup> The lack of a baseline reference value for serum IMA levels in rats, IMA binding differences in human and rat models depending on either

manual measurement or colorimetric levels, differences between human and animal serum albumin and variations of application methods are the limitations of IMA studies. It is also hard to control all of the variables that could possibly effect IMA levels as in oxidative stress conditions like malignancy, renal failure, cerebral ischemia, acute infections, surgery, anaesthesia, etc. All these issues should be taken into account for the reliability of the further studies conducted upon IMA measurements. We would like to thank Reddy et al. for their legitimate comments and contributions.

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