Letter

Increased bleeding risk associated with the use of recombinant human activated protein C in patients with advanced liver disease

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Advanced liver disease (ALD) was an exclusion criteria from enrollment in the major clinical trials of recombinant human activated protein C (APC), but is listed on the package insert as a relative contraindication rather than an absolute contraindication to APC administration [1]. There are recent reports of elevated rates of bleeding due to APC in clinical practice, particularly in patients with relative contraindications to the drug [2,3]. Since many patients who develop septic shock at Montefiore Medical Center in the Bronx, New York have ALD, we decided to evaluate whether such patients have an increased risk for bleeding during APC administration.

We retrospectively reviewed a database of all adult patients who have received APC at Montefiore Medical Center since the drug's approval. All patients at Montefiore Medical Center with severe sepsis at high risk for death and without absolute contraindications are considered eligible for APC at the discretion of the attending intensivist. Overall, 41 patients

Table 1

Patient characteristics and outcomes

Variable	ALD present ($n = 10$)	ALD absent ($n = 24$)	*P* value
APACHE II (mean (standard deviation))	29.3 (6.3)	27.8 (5.1)	0.46
Age (years) (mean (standard deviation))	50.2 (6.7)	57.4 (14.8)	0.15
Male gender (*n* (%))	6 (60.0)	13 (54.2)	0.75
Hispanic race (*n* (%))	4 (40.0)	9 (37.5)	0.89
Black race (*n* (%))	4 (40.0)	9 (37.5)	0.89
White race (*n* (%))	2 (20.0)	6 (35.0)	0.75
Major surgery (*n* (%))	2 (20.0)	10 (41.6)	0.23
Pulmonary source (*n* (%))	7 (70.0)	9 (37.5)	0.08
Gastrointestinal source (*n* (%))	1 (10.0)	8 (33.3)	0.16
Bloodstream source (*n* (%))	2 (20.0)	3 (12.5)	0.57
Skin source (*n* (%))	0 (0.0)	3 (12.5)	0.24
Genitourinary source (*n* (%))	0 (0.0)	1 (4.2)	0.51
Major bleeding episode (*n* (%))	5 (50.0)	4 (16.7)	0.04
28-day mortality	6 (60.0)	5 (20.8)	0.03

ALD, advanced liver disease as defined by the presence of chronic jaundice or ascites, cirrhosis, or portosystemic hypertension; APACHE, Acute Physiology and Chronic Health Evaluation. *P* values determined by chi-squared test or Fisher's exact test of proportions.

ALD = advanced liver disease; APC = activated protein C.

received APC at our hospital, seven of whom were not evaluable because of death soon after initiation of APC. Of the 34 remaining patients, nine had major bleeding episodes. The clinical characteristics of these 34 patients are presented in Table 1. Five out of 10 patients (50%) with ALD had major bleeding episodes, as opposed to four out of 24 patients without episodes (16.7%) ($P = 0.04$). The bleeding events experienced by the patients with ALD included two gastrointestinal hemorrhages, one intracranial hemorrhage, one major vaginal bleed, and one massive epistaxis. In a multivariate regression model that included race, sex, and Acute Physiology and Chronic Health Evaluation II score, cirrhosis remained independently associated with the risk of a bleeding event ($P = 0.02$, odds ratio = 23.5, 95% confidence interval = 1.75–315). Of the five patients with ALD who had bleeding episodes, four died within 28 days of drug administration. Interestingly, only one out of 12 patients who had undergone major surgery during their hospitalization experienced a bleeding episode (this patient did not have ALD).

Patients with ALD are at increased risk both for severe sepsis and for bleeding. These data suggest that they may be at greatly increased risk for bleeding while receiving APC. Because such patients were excluded from the major clinical trials of APC, it may be prudent to withhold therapy with APC from all patients with ALD until data from trials that include these patients, or further postmarketing data, are available.

Competing interests

The authors declare that they have no competing interests.

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