SAFETY OF ANTITHROMBIN III CONCENTRATE

To the Editor:

In their recent report, Menache et al conclude that the use of American Red Cross antithrombin III (AT III) concentrate in patients with hereditary AT III deficiency “fulfilled the criteria establishing safety.” I believe that the data presented have not excluded the possibility that transmission of human immunodeficiency virus (HIV), non-A non-B hepatitis (NANBH), or hepatitis B may have occurred. Seventy-eight percent of patients who received AT III did not have a test for HIV.

Evidence for NANBH transmission was obtained from alanine aminotransferase (ALT) estimations, as the study was conducted before hepatitis C testing. ALT data are provided only for 10 of 18 patients. In the majority of these the frequency of follow-up was inadequate. In only 11% of patients were ALT obtained at a frequency recommended by the International committee on Thrombosis and Haemostasis. Testing of ALT at monthly intervals or less is likely to miss at least 25% of cases of NANBH. Twenty percent of the patients tested had abnormal ALT, but the investigators offer alternative explanations for these. We are not told whether levels of this enzyme were abnormal before the AT III administration.

We thank Dr Makris for giving us the opportunity to clarify our position regarding the safety of Antithrombin III (Human) (AT III). We have used the word “safety” to mean “the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.”

Character of the product. Each lot of AT III used in our study was prepared from pooled plasma (140 to 600 L) representing approximately 560 to 2,400 donors. Only units nonreactive for HBsAg and anti–HIV-1 (test implemented in 1985) were used for production of AT III. However, it is well-documented that, with the exception of immune globulin products licensed in the United States, unless a viral inactivation step is included in the manufacturing process, products derived from large plasma pools are prone to transmit blood-borne viruses. Heat treatment of albumin in solution at 60°C for 10 hours has proven to be an effective method for inactivating viruses; available data indicate albumin to be a “safe” plasma derivative. To reduce the risk of virus transmission, the AT III used in our study was heated in solution (in the presence of 0.5 mol/L sodium citrate) at 60°C ± 0.5°C for 10 hours.

Hepatitis B virus (HBV). The effectiveness of the heat treatment step in reducing viral infectivity of the product used in our study was assessed in vivo in HBV susceptible chimpanzees. AT III was intentionally contaminated with 1,000 chimpanzee infectious doses (CID) of HBV, subsequently heat-treated (in the presence of 0.5 mol/L sodium citrate) at 60°C for 10 hours, and then inoculated into an HBV-susceptible chimpanzee. No evidence of HBV infection was detected over a 6-month period of close observation and laboratory testing. A control chimpanzee inoculated with an unheated aliquot of AT III intentionally contaminated with 1,000 CID of HBV developed HBV infection. Of a total of 29 patients who entered the study (18 with hereditary AT III deficiency were reported in our paper), follow-up test results were available for 24 patients (26 treatment courses) for a period of 6 to 12 months after the administration of AT III. The patient (no. 19) who seroconverted to HBV had nonreactive HBsAg test results throughout the follow-up period. This patient received two AT III lots (lot nos. 20 and 18) in January and March.

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REFERENCES


RESPONSE

We thank Dr Makris for giving us the opportunity to clarify our position regarding the safety of Antithrombin III (Human) (AT III). We have used the word "safety" to mean "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time."

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No seroconversion to HBV was noted during a follow-up period of 6 months or more for four other patients who received lot no. 20, and for two other patients who received lot no. 22. In our opinion these observations constitute a strong argument against transmission of HBV by AT III.

Human immunodeficiency virus (HIV-1). The effectiveness of the heat treatment step in reducing HIV-1 infectivity in the product used in our study was assessed in vitro. When known amounts of HIV-1 were added to AT III, heat treatment at 60°C (in the presence of 0.5 mol/L sodium citrate) inactivated more than 10^6 in vitro infectious units in 5 to 7 minutes. It seems unlikely that AT III heated in solution at 60°C for 10 hours (as opposed to 5 to 7 minutes) would carry the risk of HIV-1 transmission. No seroconversion to HIV-1 has been reported after administration of albumin (heated in solution at 60°C for 10 hours) even with lots produced before the availability of anti-HIV-1 testing.

Non-A, non-B hepatitis virus (NANBH). In response to the question raised, the answer is: yes, ALT or SGOT were elevated (in the two patients reported) before treatment with AT III. We are aware of the recommendations of the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis. We were able to implement the recommended protocol starting in 1986, but only for two patients who entered the clinical trial at this time. In 1982 no such protocol was in existence.

Conditions of the recipient. During the clinical trial only one minor side effect was noted (light-headedness) after administration of 14 lots of AT III to 29 patients who received a total of 171 infusions (432,559 IU) for 36 treatment courses. However, we are aware that as with other plasma derivatives, occasional adverse reactions may be seen.

As quoted above we also believe that absolute safety cannot be achieved. However, the body of data available on our AT III product (in vitro test results, animal model, and patient follow-up data), as well as data obtained with other “pasteurized” AT III preparations, support the “safety” of the product.

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REFERENCES

1. Section 600.3 (p) of the Food and Drug regulations [21CFR 600.3 (p)], 1989


