Whichever Anticoagulant Unit Serves Better for Evaluation of in Vivo Potency of Whale Heparin, B.P. or U.S.P. Unit?

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The correspondence between the in vitro and in vivo anticoagulative activities of beef and whale heparins was studied using the assay methods of heparin described in the British Pharmacopoeia and the United States Pharmacopeia. The coagulation time was measured by Lee-White method for 2 hours after 0.5 mg/kg of either beef or whale heparin preparation was administered intravenously to dogs.

B.P. unit of whale heparin and its in vivo potency in dogs were 1.5 times more potent than those of beef heparin, whereas U.S.P. units of whale and beef heparins were the same. Thus, better correspondence was obtained between B.P. unit and the in vivo test in dogs. The authors conclude that the B.P. assay method may be better for the clinical evaluation than the U.S.P. assay method, when the whale lung or intestine is used in place of the ox lung as the source of heparin.

In the past few years, intestinal mucosa of sheep, oxen and swine has largely replaced the ox lung as a source of commercial heparin and some swine heparin preparations were reported to have fairly high anticoagulative potency. previously the authors' research group found a potent anticoagulative activity of whale heparin which was extracted from the finback whale's lung and intestine. Some differences in biological and chemical characters of this kind of heparin were studied by a number of authors.

For the in vitro assay of heparin, the British Pharmacopoeia (B.P.) method and the United States Pharmacopeia (U.S.P.) one are being used widely at present. Which assay method will serve better for the evaluation of the clinical potency is not a serious problem so long as the source of heparin is restricted to the ox lung. However, the potency of whale heparin is different between the two assay methods. Therefore, the assay methods themselves must be re-examined before extending their application to different kinds of heparin preparations.

Fundamentally, the assay method must fulfill the following requirements: first, the in vivo anticoagulative potency in experimental animals must reflect the clinical potency in human beings; and second, the potency obtained by the in vitro assay method must be exactly proportional to the in vivo potency estimated in

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animals. The in vivo assay in animals is more preferable but it cannot be performed easily, while the in vitro test can be done everywhere and at any time. In the present investigation, the authors compared the whale and beef heparin preparations in order to determine which of B.P. and U.S.P. units would more closely correspond to the results obtained from the in vivo test in dogs.

Whale and beef heparin preparations used in this experiment were kindly assayed by Dr. de Fiebre of Wilson Laboratories using U.S.P. method and were also assayed by B.P. method in the authors' laboratory. The whale heparin was 148 U.S.P. unit/mg and 220 B.P. unit/mg, while the beef heparin was 143 U.S.P. unit/mg and 147 B.P. unit/mg.

Seven adult mongrel dogs were anesthetized by pentobarbital sodium (30 mg/kg, i.v.). 0.5 mg/kg of either kind of heparin preparation was given intravenously and the clotting time was measured by Lee-White's method before and 5, 10, 20, 30, 60 and 120 minutes after the intravenous injection. The same animals received equally each kind of heparin at one week interval. The results are shown in Fig. 1.

The area covered by the time response curve of whale heparin, measured by planimeter, was around 1.5 fold larger than that of beef heparin, and the B.P. unit of whale heparin was also 1.5 fold larger than that of beef heparin, in spite of

Fig. 1. Comparison of in vivo anticoagulative potency in dogs between beef and whale heparin preparations. Ordinate: coagulation time, and abscissa: time in minutes after intravenous administration. The vertical bars indicate standard errors of 7 experiments. Each dog received 0.5 mg/kg of whale or beef heparin with one week interval alternatively. The U.S.P. units were 148 (whale) and 143 (beef) while B.P. units were 220 (whale) and 147 (beef).
the fact that the U.S.P. unit of the both heparin preparations were almost the same. This definitely showed that B.P. unit of the whale heparin served better for measuring its in vivo potency in dogs. The clinical trial also revealed around 1.5 fold potent anticoagulative activity of the whale heparin in human beings although gingival hemorrhage may happen as a side-effect.9,10 Thus, as far as the anticoagulative potency of whale heparin preparation is concerned, there was good correspondence between the in vitro potency assayed with B.P. method modified by the authors, the in vivo anticoagulative activity in dogs and the clinical evaluations in healthy human beings and in postoperative treatment for peripheral vascular diseases.

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References