A Standard for Low Molecular Weight Heparins

D.P.	Duncan P.	Thomas
T.W.	Trevor W.	Barrowcliffe

National Institute for Biological Standards and Control, Potters Bar, Herts., UK

Prof. Hemker's editorial [1] on whether a standard is needed for low molecular weight heparin (LMWH) starts out by asking the question: 'Is there a need for a LMWH standard?', and then goes on to say that this question must be answered in the affirmative. Yet, at the end of the editorial, he argues in favour of weight per volume to indicate the strength of a LMWH, and this certainly does not require a standard. In our view, Prof. Hemker too readily dismisses the relevance of anti-Xa activity, when he claims that in vivo it has no key pharmacological importance. Certainly, recent evidence from his group, and also from Dr. Ofosu's group in Hamilton, indicates that anti-Xa activity plays only a minor role in the overall ability of heparin to inhibit thrombin formation in plasma in vitro, and that inhibition of thrombin itself may be the most important parameter. It was with these and other observations in mind that the LMWH standard was calibrated for both antithrombin and anti-Xa activities (not only anti-Xa, as implied by Prof. Hemker). However, to conclude from these in vitro observations that anti-Xa measurements are useless for comparison with in vivo events is unwarranted. This is certainly not the conclusion that is drawn by Tew et al. [2], Albada et al. [3] and Levine et al. [4]. These authors found a good correlation between anti-Xa levels, as measured in patients, and efficacy of treatment and the risk of bleeding. For example, Levine et al. [4] found a statistically significant relationship between high anti-factor Xa levels and wound haematoma and low anti-factor Xa levels and thrombosis. It is therefore surely premature for Prof. Hemker to claim that the anti-Xa action is at best an epiphenomenon, and useless for between-preparation comparisons. He claims that clinicians 'want a figure that indicates the efficacy of antithrombotic treatment and a figure, preferably a different one, on the risk of bleeding'. It would be wonderful if life were so simple, but most clinicians realize that the use of effective drugs requires a rather more sophisticated approach. He is also confusing potency and efficacy: it is not the role of biological standardization to define the efficacy of products.

Prof. Hemker believes that comparing one single property of an LMWH fraction to a single property of a standard preparation may induce a false sense of security. We think he underestimates clinicians, most of whom are well aware of the difficulties of antithrombotic therapy. In the paper immediately following Prof. Hemker's editorial, Dechavanne et al. [5] reported the successful use of 2,500 anti-Xa units of Kabi 2165 to prevent postoperative DVT in patients un-

dergoing total hip replacement. The original trial with the Choay CY216, reported by Kakkar et al. [6], used 7,500 Institut Choay anti-Xa units, with successful results. When assayed against the International Standard for Low Molecular Weight Heparin, the dose of CY216 used in the Kakkar trial is some 3,000 IU as measured by an anti-Xa assay. In other words, the doses used by Decha-vanne and Kakkar were very similar, when expressed against the LMWH standard. It seems to us far more confusing for clinicians to need to remember that 7,500 units of one preparation is equivalent to 2,500 units of another, which is the current situation. In the second paper after Prof. Hemker's editorial, Harenberg et al. [7] conclude that an anti-Xa assay (S-2222) is a reliable test for the laboratory control of LMWH. It seems that those investigators who have actually studied patients are not quite so ready as Prof. Hemker to abandon anti-Xa assays. Finally, it is hard to understand how variations in biological activity are going to be controlled if the suggestion is adopted that LMWH is prescribed on the basis of weight per volume. Fareed et al. [8], in the same issue, remark that 'large batch-to-batch variations in these LMWH's have been previously noted ...'. If no measure of biological activity is included in the drug specification, how will these variations be detected? The fact that one batch of a product labelled 20 mg may have quite different biological activities from another batch labelled 20 mg will certainly induce a false sense of security.

We have never claimed that the International Standard for Low Molecular Weight Heparin is the answer to all our problems in this difficult field. It is a first step, and we remain confident that it is a better standard than the unfractionated heparin standard for assigning potency to LMWHs. Again, nobody believes that the anti-Xa activity in any way represents the totality of the actions of heparin, but the enormous experience with this assay should not be lightly jettisoned. In our view, the use of dry weight is not an appropriate answer to this problem, since the weight per volume is not an indication of strength or potency of a chemically heterogeneous drug. Manufacturers are faced with the unenviable task of having to put a figure on the label of their product. While the potency figure may be only a partial truth, this is no reason for replacing it with something that has even less meaning.

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Duncan P. Thomas, MD,

Trevor W. Barrowcliffe, MD

National Institute for Biological Standards and

Control, Blanche Lane, South Mimms

Potters Bar, Herts. EN6 3QG (UK)

Answer to the Letter of Drs. Thomas and Barrowcliffe

It is perhaps unwise for an editor to appear as a discussant in his own journal, but I do feel that the friendly disagreement between Drs. Thomas and Barrowcliffe and me may help to shed light on the difficult issue of the standardization of low molecular weight heparins (LMWHs). I also feel that it might be possible to disentangle some of the intertwining arguments in this matter because the essential problem clearly consists of two parts. The first is: Can any LMWH be sufficiently characterized by one property? The second: If the answer is yes, then what property should that be?

As to the first question: Assume that we have a LMWH standard, let us call it S. By definition, everybody then agrees that it has S units of anti-factor Xa per mg and S U/mg of antithrombin activity. Any LMWH can be compared to the standard and then will show P U/mg of anti-factor Xa activity and Q U/mg of antithrombin activity; P and Q are not equal because the proportion of different properties varies strongly between different LMWHs. The LMWH under study therefore has P/S times the potency of the standard or Q/S times, according to what test is used for standardization. These two figures cannot be the same because it is an inherent property of the LMWHs that their properties vary according to the manufacturing procedure, unfractonated heparin being at one extreme of the scale, Choay's pentasaccharide at the other and the rest of them somewhere in between.

If we admit that standardization is possible, then we will have to decide what property we should mention on the label P or Q. The right choice is possible only if we know which of the two properties is the clinically relevant one. This, regretfully, is not yet the case. Therefore, at this moment it is premature to propose a standard together with a standard procedure in order to indicate clinical potency.

Dr. Thomas says that the standard can be used with different tests. I completely agree here, but, as shown above, with different tests and different types of LMWH the same standard will give different values. It is therefore not surprising that a large part of his letter is devoted to defending the preliminary choice of anti-Xa activity. He mentions two reasons that support this test: much experience has already been gained with it and in several studies it correlates well with clinical results. The tendency to stay with time-honoured procedures should not be carried to extremes if any progress is to be

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made at all. It must be agreed however that the number of studies in which anti-factor Xa activity seems a useful measure appears impressive (Tew, Albada, Levine, Decha-vanne, Kakkar, Harenberg [see 1 for references]). Correlation does not imply relation however. Clinical correlation can be used as an argument only for those drugs for which it has been proven to exist and cannot be used to support anti-factor Xa activity as a universal standard procedure. If one example is found in which the correlation does not hold, this – in Karl Popper's vein – invalidates the theoretical basis of the assumption.

An example may make this more clear. Imagine that for some reason estimation of protein C were an easy routine method. In all good trials of oral anticoagulation its level would correlate with good antithrombotic results. Would this then indicate that the protein C level is the property to guide oral anticoagulation? The sole example of congenital protein C deficiency tells us no. The central point of our disagreement is that the scientists from the National Institute for Biological Standards and Control feel that starting standardization at this moment would be beneficial whereas I feel that it would, for the reasons mentioned, only add to the confusion. The classical antithrombin and anti-Xa tests are carried out by adding isolated thrombin or factor Xa to the sample. Evidence is accumulating that the data thus obtained can be only of limited importance for judging the situation in plasma. Endogenously generated thrombin and factor Xa show other properties, then these factors added from outside and prothrombinase activity in plasma is hardly affected by drugs with an important anti-Xa activity [2]. Neither of these activities is even proportional

to the classical antithrombin and anti-Xa tests. In fact, recent research has shown that there are at least five different properties of heparin, distinct from classical antithrombin and anti-Xa activity, that will determine its activity in vivo, to wit: (a) the decay of endogenous thrombin; (b) the decay of endogenous factor Xa; (c) the decay of endogenous factor Xa; (d) the inhibition of prothrombinase, and (e) the susceptibility to platelet neutralizing factors. As argued above, no single method can be selected on scientifically sound grounds. We therefore should refrain from selecting a method.

I do feel that a standard for LMWHs is desirable. I also think that the state of the art at this moment is not sufficiently advanced to provide one single standard procedure that can be safely used to compare the clinical potency of different products. As long as we cannot select a best method, every preparation should be characterized as thoroughly as possible by precisely estimating all the different biological properties it has. A standard might be useful here for comparing the different laboratory procedures. The label will read like a novel, many of the properties will correlate among each other, yet only from comparing clinical results obtained with such extensively documented materials will we get an impression of the properties that are indicative of clinical potency.

Experience of 25 years in the control of oral anticoagulation has taught me that oversimplification of the issue based on insufficient understanding of the system will confuse the field and do more harm than good. I protest against the suggestion that I would underestimate clinicians. I am fully aware of the fact they understand the problem as well as most specialists do. I therefore would not dare to make them navigate on a figure of

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which they know that it cannot represent anything but an unknown correlation to the property they are actually interested in: clinical potency.

H.C. Hemker, Maastricht

Managing Editor

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Rebuttal of Drs. Thomas and Barrowcliffe

Sadly, we must agree to differ with Prof. Hemker, who is clearly a perfectionist. We would like to make just three pragmatic points in response:

Prof. Hemker claims that, because of the numerous properties of heparin, no single assay method can be selected on scientifically sound grounds. Yet heparin has been controlled satisfactorily for decades by simple pharmacopoeial assays.

His wish not to confuse the field is admirable – but does he really think that a label that ‘reads like a novel’ will contribute to be solution of the problem?

Prof. Hemker feels that a standard for LMWHs is desirable, yet he still does not answer the crucial question, which is what standard should manufacturers be using now ? We hope he would agree that, whatever biological activities of LMWH are measured, it is important that they are reproducible in different laboratories. Our data have clearly shown that much better agreement is achieved by using a LMWH standard instead of the unfractionated heparin standard.

To use his own analogy, clinicians have already embarked on their voyage of discovery, and need guidance. Prof. Hemker would say ‘don’t travel until you know precisely where you are going and by what route.’ We are offering them a crude map, but it is one that other explorers have found useful in reaching their destination.

Duncan P. Thomas

Trevor W. Barrowcliffe

Answer of Prof. H.C. Hemker

Ad. 1: What holds for unfractionated heparin, in which the proportion of its different properties (e.g. anti-IIa, anti-Xa) is more or less constant, will not hold for LMWH in which these proportions vary from preparation to preparation.

Ad. 2: Yes, because it will allow clinicians to judge a posteriori what properties correlate best with their clinical results.

Ad. 3: The very fact is that now we know just enough about LMWHs to understand that an approach that appeared to be an acceptable shortcut a few years ago must be suspected to be an oversimplification.