CLINICAL RESEARCH

Guidelines to control heparin treatment

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Abstract

With new guidelines for the control of heparin infusion rates the proportion of kaolin cephalin clotting time ratios was significantly improved compared with ratios achieved without their use. Further improvement might result from careful preparation and delivery of the infusion.

Introduction

In a previous study we showed that control of heparin treatment in our hospital was poor.[1] Kaolin cephalin clotting times outside the therapeutic range were often acted on inappropriately. Using data from that study we examined the relation between the kaolin cephalin clotting time and the rate of infusion of heparin.

Methods and results

The dose-response curves were log linear. An average dose-response relation was obtained, and for any given kaolin cephalin clotting time ratio (measured kaolin cephalin clotting time/control value) changes in the infusion rate required to give a therapeutic ratio of 1·5 were calculated. The mean infusion rate required to achieve a therapeutic kaolin cephalin clotting time was 1400 U/h (range 620-2500). Guidelines were constructed from these data (figure) and tested in 54 patients for a total of 288 heparin days. A copy of the guidelines was stamped on all the request forms for kaolin cephalin clotting times. The clotting times were measured using Diogen, Bell, and Alton, the same reagents used in the previous study (with different techniques local validation would be necessary).

The therapeutic range of kaolin cephalin clotting time ratio of 1·5-2·5 was achieved on 125 (43%) heparin days; values were below the range on 80 (28%) heparin days and above it on 83 (29%). This compares with values having been within the range on 25% of heparin days ($p<0·001$), below it on 46% ($p<0·001$), and above it on 29% in the original audit.[1] No bleeding occurred. Changes in the infusion rates achieved a therapeutic kaolin cephalin clotting time on 47% of occasions compared with 15% in the audit group ($p<0·001$). Clotting times never achieved the therapeutic range in five patients (9%) compared with 13 (29%) in the previous study ($p<0·02$). All measurements of clotting time were acted on appropriately rather than inappropriately, as had occurred in 38% of heparin days in the audit.[1] There was a significant relation between the first measurement of kaolin cephalin clotting time after the start of the infusion and the natural logarithm of the infusion rate required to achieve a therapeutic value ($r=0·87$, $p<0·001$). The required change in infusion rate predicted by this relation agreed broadly with the original guidelines for dose adjustment, suggesting that these guidelines were a reasonable guide to the mean dose relation.

Loading dose: 5000 U over 5 minutes.

Infusion: Start at 1400 U/h (eg, 8400 U in 100 ml over 6 hours). Check kaolin cephalin clotting time after 6 hours. Adjust dose according to ratio of kaolin cephalin clotting time to control value using table below.

Ratio	Change in heparin (infusion rate)
>5·0	Reduce by 500 U/h
4·1-5·0	Reduce by 300 U/h
3·1-4·0	Reduce by 100 U/h
2·6-3·0	Reduce by 50 U/h
1·5-2·5	No change
1·2-1·4	Increase by 200 U/h
<1·2	Increase by 400 U/h

Wait 10 hours before next estimation of kaolin cephalin clotting time unless ratio is greater than 5·0, in which case more frequent estimation is advisable.

Guidelines for heparin control.

Discussion

Despite the considerable interpatient variation in the pharmacodynamics and pharmacokinetics of heparin[2,3] therapeutic kaolin cephalin clotting times were achieved on 47% of occasions when the guidelines were used compared with 15% in the original audit, when they were not used. A loading dose of heparin was given to achieve

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early anticoagulation and a "pseudosteady state" after about six hours as opposed to the 10 hours (five heparin half lives) required to achieve a true steady state when a single rate infusion is given alone. Thus earlier measurement of the kaolin cephalin clotting time and dose adjustment was possible. Subsequent measurements were not made for at least 10 hours unless the kaolin cephalin clotting time was particularly long. The guidelines increased the proportion of patients with clotting times within the therapeutic range and reduced the proportion given insufficient anticoagulation and presumably more at risk of recurrence.[4]

Despite the relative precision of the guidelines there was no evidence of improved control with time. All measurements were performed in the morning, which reduced the effects of circadian variation in the response of the clotting time.[5] The apparent variation in requirements may have been related to the problems in maintaining stable intravenous infusions on a busy general ward or to normal daily variation in heparin requirements.

Although the considerable interpatient variation in response to heparin was not completely taken into account, the guidelines resulted in better heparin control. Further improvement may be achieved by careful preparation and delivery of the infusion.

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Content of low density lipoprotein receptors in breast cancer tissue related to survival of patients

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Abstract

The content of low density lipoprotein (LDL) receptors in tissue from primary breast cancers was determined and its prognostic information compared with that of variables of established prognostic importance. Frozen tumour specimens were selected, and tissue from 72 patients (32 of whom had died) were studied. The LDL receptor content showed an inverse correlation with the survival time. Analysis by a multivariate statistical method showed that the presence of axillary metastasis, content of receptors for oestrogen and LDL, diameter of the tumour, and DNA pattern were all of prognostic value with regard to patient survival.

Improved methods of predicting survival time in patients with breast cancer may be of value in the choice of treatment for individual patients.

Introduction

Breast cancer occurs in one out of 11 women in the United States and causes 19% of all deaths from cancer among women.[1] The disease runs an unpredictable course, which makes the choice of treatment for individual patients difficult. Improved predictive methods might identify high risk patients, who could be given intensive combination treatment, while low risk patients could be spared the side effects caused by extensive treatment.

Cholesterol is an important component of cell membranes. In human plasma cholesterol is predominantly found in the low density lipoprotein (LDL) fraction. Human cells have receptors for LDL. The receptor activity is regulated according to the cellular demand for cholesterol. Thus cells that synthesise steroid hormones and rapidly growing cells have high LDL receptor activities.[2] Certain tumour cells have raised LDL receptor activity in vitro.[3,4] A high uptake of LDL, mediated by receptors, in solid tumours in vivo has been shown in animals.[5-7] Whether the high LDL receptor activity is caused by the proliferation of tumour cells or by some cellular abnormality associated with the disease is not clear. The LDL receptor activity in human solid tumours is not known. We therefore investigated whether the density of LDL receptors in breast cancer tissue could be of any prognostic importance.

In breast cancer the best prognostic factors so far identified are metastases in the axillary lymph nodes and the size of the primary tumour.[8-11] Recent observations, however, have focused interest on variables of the primary tumour such as DNA pattern, proliferative index, and contents of oestrogen receptors and retinoic acid receptors[12-18] (D Killander *et al*, third European Organisation for Research on Treatment of Cancer breast cancer working conference, Amsterdam, 1983). In the present study we assessed the density of receptors for LDL and retinoic acid in specimens of frozen primary mammary carcinomas from selected patients and compared the prognostic value of these densities with already established prognostic variables such as axillary lymph node state, DNA pattern of the tumour cells, oestrogen receptor content, diameter of the tumour, and age of the patient. For the multivariate statistical analysis of the simultaneous predictive relevance of these seven variables for the prognosis of the patients, measured as survival time after diagnosis, we used partial least squares analysis with cross validation.[19-22]

Patients and methods

PATIENTS

Frozen primary breast tumours from 72 patients who had undergone surgery during 1978-9 were selected for study; 32 of the patients had died (28 had had stage I-II disease and four stage III disease at the time of surgery) and 40 were alive (39 with stage I-II disease and one with stage III disease).

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