Heparin-induced osteopenia in pregnancy

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Summary and conclusions

Multiple vertebral compression fractures occurred in a pregnant woman receiving heparin over nine months. This phenomenon may be more common than is clinically recognised and warrants careful re-examination of the indications and method of administration of anti-coagulants during pregnancy.

Introduction

Many patients receive short-term heparin anticoagulation, and the major complications of haemorrhage from excess dosage and the more idiosyncratic thrombocytopenia are well recognised. Long-term use of heparin for prophylaxis against thromboembolism is less common. Bonnar¹ and Spearing *et al.*,² however, suggested that heparin might be given throughout pregnancy by self-administered subcutaneous injections both therapeutically and prophylactically in appropriate high-risk patients. We draw attention to the risk of heparin-induced osteopenia in such cases.

Case report

A 38-year-old woman who was three weeks post partum was first seen at this hospital in February 1980 for investigation of severe low back pain that had begun suddenly during the eighth month of pregnancy.

In January 1972 the patient had had a deep venous thrombosis in the left leg, for which she had taken warfarin until July 1973. She married in 1977, and pregnancy was confirmed in May 1979. Prophylaxis was advised against thromboembolism. Because of concern about using warfarin in pregnancy, she began heparin 10 000 units subcutaneously twice daily by self-administered injection, the plasma heparin concentration (antifactor 10 activity) being maintained at less than 0.6 mU/l. Seven months later, after a few weeks of mild lumbar discomfort, there was sudden onset of severe back pain. Radiography showed appreciable osteoporosis with collapse of L2. No neurological signs were present. Heparin was continued throughout gestation, reducing to 8000 units twice daily after delivery of a healthy 3400 g infant late in December, and then stopped at the time of referral to this hospital.

Detailed history showed that pain had been present continuously for three months and was exacerbated by movement, especially forward flexion of the spine. The pain abated rapidly after stopping heparin. Initial examination disclosed pronounced spinal tenderness, maximal over L2, and there was no history of trauma or past medical disorder. Dietary assessment suggested an average calcium intake of about 600 mg daily, both before and during pregnancy, and she had never been immobilised for a long period. Serum calcium concentration was 2.5 mmol/l (10.0 mg/100 ml), phosphate concentration 1.5 mmol/l (4.6 mg/100 ml), and alkaline phosphatase activity 12 King-Armstrong units; serum thyroxine concentration, 24-hour urinary cortisol excretion, and routine estimates of renal and hepatic function were normal. Serum parathyroid hormone concentration (C terminal) was 0.5 µg/l (normal <0.5 µg/l) and 25-hydroxycholecalciferol concentration 19 nmol/l (7.6 ng/ml) (normal 15-100 nmol/l; 6.0-40.0 ng/ml).

Further radiological studies showed gross thoracolumbar spinal osteoporosis with compression fractures of T11, T12, and L2 and

prominent "codfish" changes in other vertebrae. Hand radiographs were grossly normal but the metacarpal cortical index,³ as assessed from the second left metacarpal, was 0.096, which is below the tenth centile for a standard London female population of similar age. Bone scan showed hot spots from T10 to L4 and suggested increased activity in other vertebrae. Needle biopsy of L2 yielded no evidence of malignant cells.

The patient was finally discharged taking supplemental calcium 1600 mg daily and following a programme of physiotherapy and rehabilitation; she was not prescribed an anticoagulant.

Discussion

The entity of heparin-induced osteopenia was first suggested in 1964⁴ and reported in 1965.^{5,6} Subsequently further cases were described.^{7,8} In the first report⁵ six out of 10 patients treated with subcutaneous heparin 15 000-30 000 units daily for six months or longer developed spontaneous fractures of vertebrae or ribs and showed radiological thinning of the axial skeleton. Conversely, in 107 patients receiving up to 10 000 units a day for 1-15 years no symptoms were recorded. In this second group, however, no radiological or other studies were carried out, so that unrecognised osteopenia may have been present to a less severe degree.

This probable complication of heparin has not been described before in pregnancy: indeed, such long-term heparin prophylaxis has not been widely used in pregnancy until recently. In our patient there was no suggestion of an underlying disorder, though we cannot say definitely that this was not the case. Her comparatively advanced age in pregnancy might also have been a risk factor. Nevertheless, the dose and duration of heparin treatment alone placed her in the high-risk group defined by Griffith *et al.*⁵

Heparin-induced osteopenia was reviewed by Avioli,⁹ and the mechanism for the induction of what is clearly a most unusual type of bone loss remains unclear. Heparin complexes calcium ions, acts as a cofactor for the effect of parathyroid hormone on bone resorption, and has additional effects on bone resorption even in the absence of parathyroid hormone. Further metabolic studies are being carried out to clarify and quantify this complex process, specifically in heparin-treated pregnant women.

For the present, however, we cannot assume that any bone loss encountered in this and other reported cases is completely reversible when heparin is discontinued, even though pain relief, as in our patient, apparently correlates closely with discontinuation; appropriate follow-up studies have not been reported. Even with the lower doses of heparin advocated by Bonnar,¹ subclinical, incompletely reversible osteopenia may be occurring; any deleterious effect may become apparent only many years later when the effect of age-related osteoporosis becomes superimposed on an already diminished bone mass.

A dilemma faces the obstetrician who encounters a high-risk patient needing anticoagulation. With oral anticoagulants some 15% of fetuses die of haemorrhage, and there may be a risk of teratogenesis in the first trimester.¹

It now seems possible that the risk of osteopenia might outweigh the potential prophylactic benefit of heparin in patients with a history of thromboembolism or other risk factors, though not necessarily excluding its use in patients who first develop thrombosis during pregnancy. Evaluation of the mechanism of heparin osteopenia must continue. Such studies are particularly germane to pregnancy, where increased fetal

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calcium demands exist, as a result of which the deleterious effect of heparin may be specifically augmented. A recent article on thromboembolism in pregnancy¹⁰ did not refer to the risk of osteopenia. Until the precise risks of this complication have been established the decision to use heparin must clearly be made with great care.

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Antibiotics in surgical treatment of acute abscesses

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Summary and conclusions

A four-way, double-blind, prospective trial of treatment of abscesses by incision, curettage, and primary closure with and without antibiotic cover (clindamycin injection before operation or capsules after operation, or both) was conducted. There was no appreciable difference in mean healing time between the patients given both the antibiotic injection and the antibiotic capsules and those given the injection and placebo capsules, whereas healing times in those given the placebo injection and antibiotic capsules or placebo only were appreciably longer. Four of the patients who were not given the antibiotic injection developed bacteraemia; one patient who was given the antibiotic injection also developed a bacteraemia, but this was caused by clindamycin-resistant bacteria.

These results show that a single injection of an effective antibiotic before operation is sufficient to protect the patient against bacteraemia and permit optimum healing.

Introduction

Before the discovery of antibiotics an acute abscess was usually treated by applying a poultice to draw the pus to the surface. Once the abscess was "ripe" or "pointing" it was incised and the cavity packed with a cotton wick to encourage healing from the depth of the cavity outwards. After the introduction of antibiotics Ellis¹ showed that pus could be released safely and the abscess wall removed by curettage as soon as the diagnosis was made, provided that antibiotic was combined with the surgical treatment. Subsequently he showed that the antibiotic was so effective in combating the infection that the abscess cavity could

be closed by primary suture. The antibiotic regimen he used complied with the current dogma that if an antibiotic has been prescribed treatment must continue for five days to discourage development of resistant strains of micro-organisms. He gave an intramuscular injection of antibiotic one hour before operation and a five-day course of treatment by mouth after operation. The hypothesis behind the use of antibiotics was that the blood that filled the freshly evacuated and curetted abscess cavity would be laden with antibiotic and would sterilise the contents, thus permitting safe suture. This attractive idea has never been proved to be true and is still regarded with scepticism even though the results of this method of treatment have established its efficacy.²⁻⁶

Recently Rutherford *et al*⁷ suggested that primary closure after curettage of an abscess is safe and effective without the use of an antibiotic, even though many surgeons object to curettage because of the danger of causing a bacteraemia. We decided, therefore, to test the theoretical basis of this method and determine the necessity or otherwise of antibiotics by a four-way, double-blind, prospective trial using evidence of postoperative bacteraemia or septicaemia and prolonged healing times to show unsatisfactory results.

Patients and methods

Phials of antibiotic or placebo were prepared with only their serial numbers to distinguish them. Similarly, capsules of antibiotic or placebo were prepared with an identical appearance. The antibiotic used was clindamycin. The intramuscular injection contained 300 mg clindamycin phosphate and the capsules 150 mg clindamycin hydrochloride. Patients who had been given lincomycin or clindamycin in the past week were excluded from the trial. Packs were prepared and labelled with serial numbers; each pack contained a phial and 16 capsules, one capsule to be taken six-hourly for four days after operation. Neither the doctor nor the patient was aware of the true nature of the contents of each pack. After 80 patients had completed their treatment the code was broken, and the patients were then found to have been randomly divided into the following groups.

Group 1—Antibiotic injection one hour before operation; antibiotic capsules for four days after operation.

Group 2—Antibiotic injection one hour before operation; placebo capsules for four days after operation.

Group 3—Placebo injection one hour before operation; antibiotic capsules for four days after operation.

Group 4—Placebo injection one hour before operation; placebo capsules for four days after operation.

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