effects of metoprolol and propranolol on the peripheral circulation occur after long-term oral dosing.¹⁰ Our findings show differences between the effects of metoprolol and propranolol on skin temperature, skin blood flow, and muscle blood flow both at rest and after exercise in normal subjects and support, by direct measurement of tissue blood flow, the hypothesis that cardioselectivity may be an important property of beta-blockers if these are to be given to patients with established peripheral vascular disease. Our results, in common with those on airways resistance,¹ show that cardioselectivity is not an absolute property and that metoprolol has a significant effect in reducing post-exercise muscle hyperaemia. This effect, however, is much less pronounced than that of propranolol, which also reduces skin temperature, skin blood flow, and resting muscle blood flow.

Our results in four patients with benign essential hypertension showed similar differences between the two beta-blockers, with the exception that metoprolol also caused a significant reduction in skin blood flow.

These results, taken in conjunction with clinical reports of peripheral gangrene in hypertensive patients being treated with beta-blockers,⁷⁻⁸ suggest that metoprolol has important advantages over propranolol in its effect on the peripheral circulation. Although technical factors limited our observations

on exercise to post-exercise hyperaemia, we believe that the differences we have shown between the effects of the two drugs are significant. Further studies on the effects of these and other beta-blocking drugs on muscle blood flow *during* graded physical exercise are clearly needed.

We are grateful to our general-practitioner colleagues who allowed us to study their patients, and to our subjects for their forbearance.

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Liver enzyme concentrations as measure of possible infectivity in chronic asymptomatic carriers of hepatitis B

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Summary and conclusions

Fifty-two British-born blood donors who were chronic carriers of hepatitis B surface antigen (HBsAg) were tested for the presence of hepatitis B e antigen (HBeAg) and antibody to HBeAg by an immunoradiometric assay. The presence of HBeAg was closely associated with a slight rise in serum liver enzyme concentrations, a high HBsAg titre, and male sex.

We suggest that the finding of persistently raised serum liver enzyme concentrations in an asymptomatic HBsAg carrier might be useful as a likely indicator of HBeAg and high infectivity.

Introduction

Hepatitis B surface antigen (HBsAg), antibody to HBsAg, hepatitis B core antigen, and antibody to core are well-

established markers of past or present infection by hepatitis B virus. The e-antigen (HBeAg) system described by Magnius¹ has aroused considerable clinical interest with the finding of an association between HBeAg and high infectivity in vertical² and horizontal³ transmission.

When an undiagnosed carrier of HBsAg is discovered in a community—particularly a carrier working in medical care—the question naturally arises whether that person is likely to be infectious. One of the most useful indices of potential infectivity,⁴⁻⁵ but one that is not easy to assay in a routine laboratory investigation, is the e antigen. The presence of HBeAg has been used as an indicator of liver disease,⁶ and among carriers those with chronic liver disease appear to be the most infectious.⁷ In this study we have correlated the presence of HBeAg in chronic asymptomatic carriers with raised serum liver enzyme concentrations in an attempt to assess indirectly the usefulness of liver enzyme monitoring as an indicator of high infectivity.

Subjects and methods

Blood Donors—British-born blood donors were screened for HBsAg by reverse passive haemagglutination (RPHA; Hepatest, Wellcome Reagents Ltd). Samples for confirmation were obtained from all who were HBsAg-positive. The first and second, or subsequent, specimens were titrated in parallel; donors were excluded from the study if they had a greater than twofold difference in HBsAg titres over a minimum of three months. So that we could make comparisons with results from a transfusion centre abroad that used counterimmigration electrophoresis to detect HBsAg, we selected only RPHA positive donors who were also positive by this technique for inclusion in the series. The *ad* or *ay* subtype was determined by immunoradiometric assay.⁸

Detection of HBeAg and antibody to HBeAg (anti-HBe)—HBeAg and

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anti-HBe were initially assayed by the immunodiffusion technique described by Tedder.⁹ All sera were subsequently tested by solid-phase sandwich immunoradiometric assay for HBeAg and anti-HBe (e-RIA) in a manner similar to that described by Frösner *et al.*¹⁰ The globulin fraction (40% ammonium sulphate precipitate) from human serum containing anti-HBe was used to coat polystyrene tubes. A 100 μ l sample of serum for testing was dispensed into the tube and maintained at room temperature overnight. After washing, ¹²⁵I-labelled IgG (Bolton and Hunter reagent; Radiochemical Centre, Amersham) from human serum containing anti-HBe was added. After four hours' incubation at room temperature the tubes were washed and the radioactivity counted. Sera that gave an increased binding of labelled IgG were classified as containing HBeAg only if, in a confirmatory test, this effect could be neutralised by human serum containing anti-HBe but not by normal serum. The assay of anti-HBe was based on the reduction of the binding by a standard amount of HBeAg when anti-HBe was added. Sera were considered to contain anti-HBe when they caused a significant reduction in binding.

Serum liver enzymes—Concentrations of aspartate transaminase and alanine transaminase were assayed on a Reaction Rate Analyser (LKB 8600) at 35°C. They were defined as abnormal when the values exceeded 30 IU/l; this figure is the mean plus two standard deviations for enzyme estimations in about 1000 normal blood donors (VM, unpublished data).

Results

We found a clear association between HBeAg and raised liver enzyme concentrations (table I), and the ranges of liver enzyme values differed between sera containing HBeAg and those containing anti-HBe (fig 1). In all instances the results of immunodiffusion were confirmed by e-RIA; the greater sensitivity of e-RIA permitted reclassification of 13 of the 15 sera previously found negative by immunodiffusion as containing HBeAg or anti-HBe. Of these sera, 11 were positive for anti-HBe and only two for HBeAg.

All sera containing HBeAg had high RPHA titres (fig 2), which agrees with previous findings.¹¹ Nevertheless, there was considerable

TABLE I—Relation of HBeAg and anti-HBe to raised serum liver enzyme concentrations in group of 52 asymptomatic carriers of HBsAg. Figures are results obtained by immunoradiometric assay (figures in parentheses are results of testing same sera by immunodiffusion)

	No positive for HBeAg	No positive for anti-HBe	No negative
AST and ALT concentrations { Both normal Either or both raised	1 (1) 13 (11)	33 (23) 3 (2)	2 (12) 0 (3)

AST = Aspartate transaminase. ALT = Alanine transaminase.

FIG 2—Distribution of RPHA titres and raised serum liver enzyme concentrations among 52 asymptomatic carriers of HBsAg. HBeAg and anti-HBe were detected by immunoradiometric assay.

□ = Carriers with normal enzyme concentrations (AST and ALT < 30 IU/l). ▨ = Carriers with raised enzyme concentrations (> 30 IU/l).

TABLE II—Number of male and female HBsAg carriers positive and negative for HBeAg and anti-HBe

	No positive for HBeAg	No positive for anti-HBe	No negative	Total
Male carriers	13	21	2	36
Female carriers	1	11	2	12

overlap of RPHA titre between this group and sera containing anti-HBe. There was no difference in subtype distribution between sera containing HBeAg or anti-HBe; among the HBeAg-positive carriers 11 were subtype *ad* and three subtype *ay*, and among the carriers positive for anti-HBe 31 were *ad* and five *ay*. Proportionately more male carriers than female were HBeAg-positive (table II).

Discussion

Nath *et al* suggested that the *ay* subtype is more commonly associated with HBeAg and high infectivity than the *ad* subtype¹²; we did not find this association in our small study of a British blood-donor population. Equal numbers of men and women donated blood, and, although the tendency for the HBsAg carrier state to develop after infection is the same in both sexes,¹³ we found a three to one preponderance of male carriers. Similar ratios have been found in several other populations.¹⁴ We found that a greater proportion of male carriers was HBeAg-positive (table II); there was no obvious explanation for this, but it may have reflected a larger number of more recent initial infections in the men. The apparent low infectivity of the European HBsAg-carrier mother¹⁵ may be associated with the low incidence of HBeAg in female carriers.

FIG 1—Distribution of liver enzyme concentrations in 50 asymptomatic carriers of HBsAg who were positive for HBeAg or anti-HBe by immunoradiometric assay. A raised value is defined as greater than 30 IU/l (dashed line).

AST = Aspartate transaminase. ALT = Alanine transaminase.

All hepatitis B carriers who were HBeAg-positive had high titres of HBsAg; this could not be used as a reliable indicator of the presence of HBeAg, however, because some of the carriers with anti-HBe also had high HBsAg titres. Generally it has been found that many HBsAg carriers have neither HBeAg nor anti-HBe, which reflects the relative insensitivity of immunodiffusion—for example, in our study 29% of the carriers were e-negative by this test. This number of unclassifiable carriers has made it difficult to evaluate the relation between HBeAg and raised liver enzyme concentrations reported by Maynard *et al*¹⁶ and Polesky and Hanson.¹⁷ By using the more sensitive e-RIA in addition to immunodiffusion we could confirm their observations and show a more precise relation between the presence of HBeAg and raised enzyme concentrations.

In acute hepatitis B infections serum liver enzyme concentrations are generally much higher than those in carriers and HBeAg is only transiently present. In chronic asymptomatic carriers persistently, though modestly, raised liver enzyme concentrations appear to be a useful indicator of the presence of e antigen and thus of probable infectivity. Indeed, it is interesting to compare the accuracy of using either immunodiffusion or raised enzyme concentrations to identify the HBeAg-positive carriers. Immunodiffusion identified 12 of the 14 HBeAg-positive sera, whereas 13 were identified by finding raised enzyme concentrations, though at the cost of three anti-HBe sera being incorrectly classified.

Testing for the presence of HBeAg is practicable only for specialised laboratories; on the other hand, estimating liver

enzyme concentrations is a routine determination in any general hospital. We consider that when assessing the potential infectivity of an indigenous HBsAg carrier in the UK estimating liver enzyme concentrations is a simple and accurate alternative to the specific tests for HBeAg.

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Haemodynamic effects of buprenorphine after heart surgery

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Summary and conclusions

The effect of buprenorphine on the cardiovascular system was examined in 11 patients during the period of reduced cardiac reserve after open-heart surgery. Within 10 minutes of giving the full analgesic dose (5 µg/kg) intravenously the mean heart rate had fallen significantly by six beats/min. Although in two patients the mean arterial pressure fell by 24 mm Hg, there was no overall change in mean arterial pressure, cardiac output, or peripheral resistance. In a further six patients buprenorphine was used successfully as the sole analgesic after open-heart surgery.

Buprenorphine appears to be safer than morphine for use in patients with reduced cardiac reserve and is of similar analgesic efficacy.

Introduction

Buprenorphine, a synthetic derivative of the opium alkaloid thebaine, is a strong new analgesic currently undergoing clinical trial. Initial experience suggests that it has little tendency to produce addiction.¹ A dose of 0.6 mg gives the same degree of pain relief as 15 mg morphine and lasts up to eight hours.² Morphine is a vasodilator and may cause hypotension in the presence of reduced cardiac reserve or hypovolaemia.³ This effect is well known after cardiac surgery. Initial studies suggested that buprenorphine exerts less effect on the cardiovascular system than morphine. These studies, however, were carried out on animals,⁴ volunteers,⁵ and postoperative patients⁶ whose cardiovascular systems were normal. We decided to examine the cardiovascular effects of buprenorphine in the period of reduced cardiac reserve after open-heart surgery. The study protocol was approved by the hospital's ethics committee, and all patients gave written informed consent before operation.

Patients and methods

Eleven patients were studied within 24 hours after open-heart surgery; their average age was 54 years (range 32-67 years) and average weight 66 kg. Operations comprised valve replacement, correction of

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