oxidative function. Our results suggest that ranitidine has an advantage over cimetidine in being free of this effect.

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# Radioimmunoassay of serum creatine kinase BB as index of brain damage after head injury

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## Summary and conclusions

**Brain-type creatine kinase isoenzyme (CK-BB) was measured by radioimmunoassay in the serum of 54 patients with head injuries. CK-BB was not detectable in 476 out of 1006 controls, the remaining 530 normal samples containing a mean of 1·5±SD0·75 μg/l. The mean CK-BB concentrations in patients with mild, moderate, and fatal head injuries were all significantly higher than the control value ($p < 0.01$ in each instance). Patients with serious head injury had serum concentrations many times the normal value, in two cases within 30 minutes after impact. Fatally injured patients continued to have high serum concentrations several days after injury. In less serious cases values approached normal within two or three days. Every patient with evidence of cerebral laceration, bruising, or swelling had a serum CK-BB concentration above normal. Raised concentrations were found in 14 out of 22 patients with concussion only.**

**The serum CK-BB concentration appears to be a sensitive index of brain damage and may prove useful in the management and follow-up of head-injured patients.**


## Introduction

A biochemical index of the extent of brain damage might be of great value in assessing and managing patients with head injury. Several proteins have been measured in serum and cerebrospinal fluid after trauma, including lactate dehydrogenase isoenzymes,[1-6] creatine kinase isoenzymes,[7 8] and myelin basic protein.[9 10] Though such studies usually show a correlation between the serum concentration of the marker protein and the extent of the cerebral lesion, the methods may not be sensitive enough to monitor minor degrees of brain damage, and no one marker protein has become established in patient care. Brain-type creatine kinase isoenzyme (CK-BB) has been measured in head injuries by fluorescence[7] and by spectrophotometry.[8] Bell *et al*[11] measured CK-BB by radioimmunoassay in serum and cerebrospinal fluid from patients with neurological disorders and found significantly increased mean values in those with acute cerebrovascular accidents, patients with prolonged alterations of consciousness, and in a single patient with head injury. We developed a similar radioimmunoassay for CK-BB and found significantly raised mean serum concentrations in patients with dementia and also isolated raised values in patients with epilepsy, cervical myelopathy, and cerebellar degeneration.[12] Apart from neurological disorders radioimmunoassay has shown raised serum CK-BB concentrations in malignant diseases.[13]

Radioimmunoassays for creatine kinase isoenzyme estimation are reportedly about 1000 times more sensitive than conventional spectrophotometry[14] and furthermore recognise enzymically inactive but immunologically reactive protein. We have therefore used radioimmunoassay to measure CK-BB in the serum of 54 patients with head injury to see whether the concentration is a sensitive index of brain damage.

## Patients and methods

The 54 patients were divided into three groups according to the early outcome (death or discharge).

*Group 1* comprised 25 patients with mild head injury resulting in loss of consciousness for under 10 minutes. Three patients had transient neurological signs detectable after they regained consciousness, but the remaining 22 were concussed only. All patients fully recovered and showed no residual disability on discharge.

*Group 2* comprised 19 patients with serious head injury resulting in some residual deficit on discharge.

*Group 3* comprised 10 patients with isolated severe head injury resulting in death.

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Most of the head injuries were sustained in road-traffic accidents. Patients with multiple injuries or suspected abdominal injuries were excluded. No patient had evidence of malignancy or of pre-existing neurological disorder. Control samples were obtained from 1006 blood donors and normal volunteers.

The CK-BB radioimmunoassay was performed exactly as described.[12] Intra-assay and interassay variations were 4·5% and 10·5% respectively. Sera from patients with head injury were either separated and assayed immediately or stored at −70°C for up to two weeks before assay, immunoreactivity being unaffected by storage. The immunoreactivity in the sera of patients with head injuries diluted out in parallel with the standard curve of the radioimmunoassay. The detection limit of the assay corresponded to a serum concentration of 0·5 μg/l.

Significance of differences in means between different groups was assessed with Student's *t* test.

## Results

Of the 1006 control sera, 476 (47·3%) contained no detectable CK-BB. These comprised 258 (57·7%) of the 447 samples from women and 218 (39·0%) of the 559 samples from men. The mean serum concentration in the 189 women with measurable immunoreactivity was 1·44 ± SD 0·71 μg/l and in the 341 men with detectable immunoreactivity 1·36 ± 0·88 μg/l. The controls were aged 18-70 years, and in neither sex did the detectable mean CK-BB concentration differ significantly with age group (≤30, −50, −70). Four control sera (0·003%) contained concentrations of over 3·0 μg/l; three were from men aged 40, 42, and 43 years, whose values were 5·3, 5·0, and 5·8 μg/l respectively, and one was from a 21-year-old woman, whose concentration was 8·2 μg/l. A value of 3·0 μg/l was taken as the upper limit of normal.

Figure 1 shows the serum CK-BB concentrations in the three groups of head-injured patients. Patients with mild head injury (group 1) had a mean concentration of 4·57 ± SD 2·55 μg/l, those with serious head injury resulting in some residual deficit (group 2) a mean concentration of 11·21 ± 1·27 μg/l, and those with fatal head injury

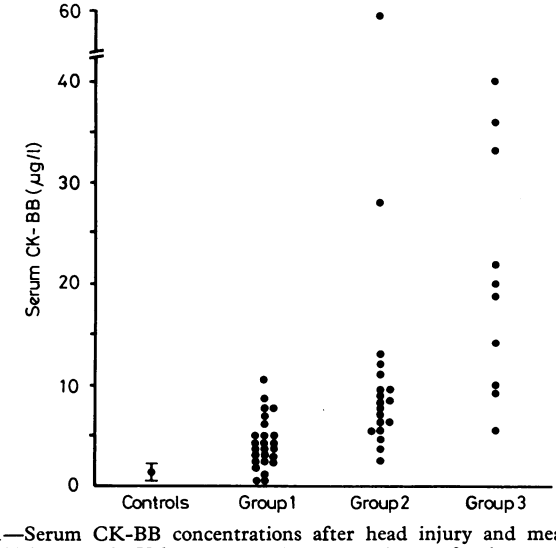


FIG 1—Serum CK-BB concentrations after head injury and mean value (±SD) in controls. Values measured one to 12 hours after impact in group 1, 30 minutes to 24 hours in group 2, and 30 minutes to 72 hours in group 3.

(group 3) a mean concentration of 20·9 ± 11·9 μg/l. The mean concentration in group 3 was significantly higher than the means in groups 1 and 2, and all three means were significantly higher than the control value ($p < 0·01$ in each instance).

*Fatal head injury*—The 10 patients in group 3 were aged 18-76 years, and all suffered severe generalised or localised cerebral laceration or bruising and died within one and a half hours to nine days after admission. In each case the head injury was the only injury present. All but one of the patients were unconscious on admission. The earliest available measurement was 33 μg/l in a patient 30 minutes after injury, two other patients having values of 33 and 40 μg/l within one hour of injury. A fourth patient died on the ninth day from continuing cerebral oedema. His initial serum CK-BB concentration of 10 μg/l decreased over five days to 3 μg/l but rose again to 10 μg/l on day 6 and was 8 μg/l on the day of death.

*Serious head injury with some residual deficit*—The 19 patients in group 2 were aged 7-75 years, and initial CK-BB concentrations were obtained 30 minutes to 24 hours after injury (14 measurements within 12 hours). Fifteen patients were unconscious on admission, responding only to painful stimuli. Most of the 19 patients showed moderate generalised or localised bruising on CT scanning with corresponding high serum CK-BB values. A patient struck by a wing mirror had the highest CK-BB concentration recorded (60 μg/l), which was estimated 30 minutes after injury. In one patient the clinical deterioration on day 8 and the subsequent temporal lobe resection were reflected by an increase in CK-BB from a steady 5 μg/l to 8 μg/l on day 8 and to 23 μg/l after operation (fig 2). Subsequent values were between 6 and 10 μg/l and coincided with a continuing poor clinical state (eye opening/motor response/verbal response score 7, Glasgow coma scale).

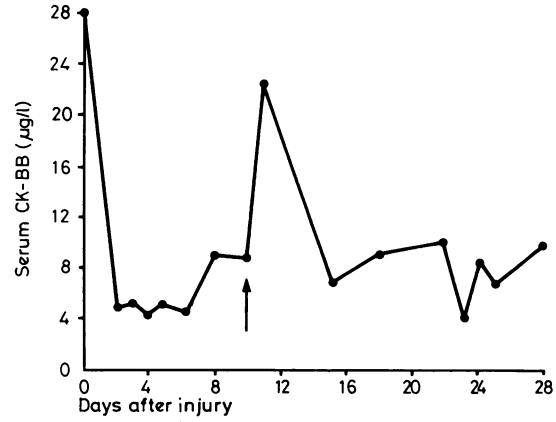


FIG 2—Serial serum CK-BB measurements in patient in group 2 (serious head injury). Patient was unconscious on admission with serum CK-BB concentration 28 μg/l on day 1. Further deterioration occurred between days 6 and 8, followed by temporal lobe resection on day 10 (arrowed).

*Mild head injury*—The 25 patients in group 1 ranged from 8 to 55 years of age, and initial serum CK-BB concentrations were measured within one to 12 hours after injury. Most of the patients were injured in minor road-traffic accidents, six were injured while fighting or engaged in sport, while four had falls. No patient was unconscious for more than 10 minutes, and most had post-traumatic amnesia for under 30 minutes. The only case of proved cortical laceration in this group was a 10-year-old boy kicked by a horse; his CK-BB concentration of 8·3 μg/l at one hour fell to 5 μg/l at 48 hours, with definite objective neurological improvement. A further patient with mild brain injury had a concentration of 8·3 μg/l within one hour of injury. Fourteen out of 22 patients with concussion had values above 3 μg/l compared with 4 (0·003%) of the controls.

## Discussion

Other attempts to measure CK-BB in serum after head injury[7 8] have relied on spectrophotometric procedures, which lack immunological specificity and are not usually sensitive enough to detect the protein in normal serum or in patients with concussion. Our radioimmunoassay detects high degrees of immunoreactivity in the serum after head injury. While large intestine and prostate contain appreciable amounts of CK-BB,[12] high concentrations in patients with injuries confined to the head and the correlation with the degree of cerebral damage point to the brain as the source of the circulating CK-BB. Immunoperoxidase techniques localise CK-BB to astrocytes.[15] Serum CK-BB concentrations of up to 6 μg/l may be found in dementia and cerebellar degeneration,[12] but none of the present

patients had any evidence of neurological disorders before head injury.

Serum CK-BB concentrations apparently increase rapidly after serious head injury and may reach 30 to 40 times the mean control value (fig 1). Of patients for whom serial measurements were available at least three in the fatally injured group continued to have concentrations five to 10 times normal three to six days after injury. In less serious cases CK-BB concentrations approached normal within two or three days. Hence such preliminary serial CK-BB measurements appear to correlate with clinical improvement, and a high initial reading suggests severe cerebral injury. Possibly concentrations of diagnostic and prognostic value would be obtained if patients with serious head injury were assayed for serum CK-BB within six hours of injury and again after four to six days. The use of CK-BB concentrations as an indicator of continuing or increasing cerebral oedema would require daily samples, but as little as 200 μl of serum (or plasma derived from daily blood gas measurement) would suffice.

Serum CK-BB detected by radioimmunoassay is apparently a sensitive biochemical indicator of brain injury. Not one of our patients with evidence of brain laceration, bruising, or swelling failed to show a concentration above normal. CK-BB is a soluble cytoplasmic protein which presumably can diffuse readily into the blood stream and is consequently detectable even in patients with concussion or minor head injury. Further measurements of this protein as a potentially clinically useful adjunct in the management and follow-up of head injury appear to be justified, and such a study is in progress.

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# SHORT REPORTS

## Fibreoptic bronchoscopy: is sedation necessary?

Fibreoptic bronchoscopy is now carried out in chest units all over Britain. Opinions differ on the premedication required and the need for general anaesthesia. This study attempts to assess patients' reactions to bronchoscopy without sedation or, in a few cases, with very mild sedation.

### Patients, methods, and results

The study comprised 100 consecutive routine diagnostic bronchoscopies. All patients were premedicated with atropine 0·6 mg and two benzocaine lozenges. Seven patients were given diazepam 10 mg intramuscularly because they appeared very nervous or requested it. All were fully conscious and capable of seating themselves in the dental chair used for the procedure. The nose was sprayed with cocaine 5% and the pharynx with lignocaine 4%. The instrument was passed transnasally. Lignocaine 2 ml was instilled over the vocal cords and a further 2 ml into the trachea, which was then entered. After inspection of the bronchi tissue for histological examination was taken in 60 cases before withdrawing the instrument. Patients were asked to complete a small questionnaire (table) and were then allowed to return home or to the ward.

Out of the 100 patients 95 found the procedure "no bother" or "a bit uncomfortable," a response which was even more favourable than expected. Four recorded worse impressions of the procedure and may be said to have found it unacceptable. In one patient copious vomiting over the operator caused the procedure to be abandoned. Ninety-two patients stated their willingness to have a repeat examination done in the same way if advised. Six asked for a general anaesthetic, and one rejected any possibility of a second bronchoscopy. This question was asked to try to establish whether patients were merely trying to please in their comments. The replies suggested that they were mostly being honest. There were no serious

*Questionnaire given to patients after fibreoptic bronchoscopy*

You have just had an examination which we call bronchoscopy. We would like to know how you found it. Please mark with a cross the comment which comes nearest to your feelings about it.

*Did you find the examination*:

- ☐ No bother?
- ☐ A bit uncomfortable?
- ☐ Bad?
- ☐ Very bad?
- ☐ The worst experience you have ever had?

*If you had to have the examination again would you want it done*:

- ☐ The same way?
- ☐ Only under a general anaesthetic?
- ☐ Not at all?