Metabolic effects of bicarbonate in the treatment of diabetic ketoacidosis

P J HALE, J CRASE, M NATTRASS

Abstract

The effect of intravenous bicarbonate on the changes in intermediary metabolites during the initial treatment of diabetic ketoacidosis was examined in 16 patients. The results were compared with the changes seen in 16 patients receiving intravenous saline. Infusion of 150 mmol (mEq) bicarbonate significantly delayed the fall in blood lactate, lactate:pyruvate ratio, and total ketone bodies observed in the saline treated group. No difference in the rate of fall of blood glucose concentration was found.

There is no metabolic indication for the use of intravenous bicarbonate in the treatment of diabetic ketoacidosis.

Introduction

The use of intravenous bicarbonate in the treatment of diabetic ketoacidosis is controversial. Acidosis affects the cardiovascular system causing negative inotropism[1 2] and peripheral vasodilatation,[3] which may exacerbate hypotension and hypothermia. The risk of ventricular arrhythmias may be increased in metabolic acidosis,[4] and with very low pH respiratory depression may occur.[5]

Correction of the acidosis by bicarbonate, however, has not been shown to correct these abnormalities and is associated with certain risks. Without adequate replacement therapy hypokalaemia may result,[6] and cerebral oedema has been linked to bicarbonate administration,[7 8] although the evidence is inconclusive.[9]

Further reservations about bicarbonate administration concern the effect on the oxyhaemoglobin dissociation curve. Low 2,3-diphosphoglycerate concentrations shift this curve to the left,[10] which is counteracted by acidosis inducing a rightward shift.[11] Rapid correction of acidosis with bicarbonate may impair oxygen delivery to tissues resulting in tissue hypoxia,[12] and experiments in animal models of diabetic ketoacidosis support this view.[13]

The present study was undertaken in order to clarify the effect of bicarbonate on the response of intermediary metabolites during treatment of diabetic ketoacidosis.

Patients and methods

Thirty eight consecutive patients with diabetic ketoacidosis were studied. Diabetic ketoacidosis was diagnosed if on presentation the patient showed symptoms and signs of severe uncontrolled diabetes necessitating emergency hospital admission and treatment with intravenous fluids and insulin.[14] Biochemical confirmation of the diagnosis was given by a capillary pH of $\leq 7{\cdot}20$, a plasma bicarbonate concentration of <15 mmol(mEq)/l, and ketonuria ($\geq ++$ on testing with Ketostix).

All patients were rehydrated with saline (150 mmol(mEq)/l), with or without sodium bicarbonate (150 mmol/l), and intramuscular insulin. In five patients blood glucose concentration fell to <14 mmol/l (<250 mg/100 ml) before the end of the study, necessitating a change in intravenous fluid to glucose (5% dextrose). In view of the effects of glucose infusion on the intermediary metabolites measured these patients are excluded. In one other patient samples were unsatisfactory for analysis.

The 38 patients were allocated at random to two groups, one given bicarbonate and the other saline. With the exclusion of the six patients noted above, 16 (six male, 10 female) with a mean age of 47 years (range 15-80) received bicarbonate and 16 (eight male) with a mean age of 41 years (range 15-74) received saline. All patients were previously diagnosed but two in the bicarbonate group had not received insulin before, previous treatment having been with sulphonylureas; neither was taking a biguanide on admission.

One patient died 36 hours after admission. She was receiving corticosteroids for longstanding multiple sclerosis and died of septicaemia. There was no major difference in precipitating factors of diabetic ketoacidosis between the groups, though a specific cause was identified in only about half of the patients.[9]

In all cases treatment was begun in the casualty department with 1 l saline (150 mmol/l) in the first hour and 20 U neutral porcine insulin (Actrapid, Novo Laboratories, Basingstoke, Hampshire) by intramuscular injection. Patients were then transferred to the ward. With the administration of the next hourly injection of insulin (6 U) sodium bicarbonate (150 mmol/l) or sodium chloride (150 mmol/l) infusion was instituted (time zero). Over the next 60 minutes 1 l fluid was infused. At 60 minutes 6 U neutral porcine insulin was given followed in the next 60 minutes by 1 l saline (150 mmol/l) in all patients.

Blood samples were withdrawn at 0, 30, 60, and 120 minutes through an indwelling Teflon cannula inserted into the other arm and kept patent by flushing with 2 ml saline (150 mmol/l).

Capillary blood for measurement of pH, partial pressure of carbon dioxide, and bicarbonate concentration was obtained by finger prick and collected into heparinised tubes (Corning Medical, Medfield, MA) and analysed using a Corning 175 blood gas analyser.

At each sampling approximately 2 ml venous blood was withdrawn and deproteinised immediately in 5% vol/vol perchloric acid.

Blood glucose, lactate, pyruvate, 3-hydroxybutyrate, glycerol, and alanine concentrations were assayed in the perchloric acid extract by continuous flow fluorometric techniques.[15] Blood acetoacetate was measured in the perchloric acid extract within 36 hours by spectrophotometry.[16]

The sum of 3-hydroxybutyrate and acetoacetate concentrations is referred to as total ketone bodies.

Results are expressed as mean and standard error of the mean (SEM) and differences between groups were sought using Wilcoxon's rank sum test for unpaired data.[17]

The study was approved by the ethical committee of the Central Birmingham Health District. Informed consent could not be obtained.

Results

The initial pH in the bicarbonate treatment group was 6·85-7·18 (mean 7·05) and in the saline treatment group 6·85-7·20 (mean 7·06). Both groups showed a rise in pH at 120 minutes, but this was significantly greater in the patients given bicarbonate (to 7·23 *v* 7·12; $p<0{\cdot}01$).

Capillary blood bicarbonate concentration rose from a mean of 7 mmol (mEq)/l (range 2-11 mmol/l) to 12 mmol/l (range 5-22 mmol/l) in patients given bicarbonate and from 7 mmol/l (3-15 mmol/l) to 9 mmol/l (4-16 mmol/l) in the saline group. The rise was significantly greater ($p<0{\cdot}01$) in the bicarbonate treated group.

Diabetic Clinic, General Hospital, Birmingham B4 6NH

P J HALE, MA, MRCP, research registrar
J CRASE, AIMLS, senior medical laboratory scientific officer
M NATTRASS, PHD, MRCP, consultant physician

Correspondence to: Dr M Nattrass.

Blood intermediary metabolite concentrations (mmol/l) and ratios at start of study period (time 0). Results expressed as mean, (SEM), and [range]

	Glucose	Lactate	Pyruvate	Lactate: pyruvate	Alanine	3-Hydroxy butyrate	Acetoacetate	Total ketone bodies	3-Hydroxybutyrate: acetoacetate	Glycerol
Saline	35 (5) [17-76]	2·90 (0·57) [0·99-8·19]	0·16 (0·02) [0·08-0·38]	16·6 (0·9) [11·7-22·8]	0·30 (0·02) [0·14-0·47]	9·0 (0·6) [5·6-13·3]	3·7 (0·3) [2·1-5·6]	12·6 (0·7) [9·2-18·6]	2·5 (0·1) [1·3-3·6]	0·26 (0·05) [0·08-0·69]
Bicarbonate	40 (4) [16-73]	3·42 (0·78) [1·13-12·29]	0·17 (0·03) [0·07-0·41]	18·4 (1·4) [10·0-31·4]	0·30 (0·03) [0·16-0·62]	8·5 (0·5) [6·6-12·7]	3·5 (0·3) [1·4-5·8]	12·1 (0·6) [9·5-18·4]	2·7 (0·3) [1·5-6·5]	0·34 (0·07) [0·12-1·14]
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. Lactate: 1 mmol/l ≈ 9 mg/100 ml. Pyruvate: 1 mmol/l ≈ 8·8 mg/100 ml. Alanine: 1 mmol/l ≈ 8·9 mg/100 ml. 3-Hydroxybutyrate: 1 mmol/l ≈ 10·4 mg/100 ml. Acetoacetate: 1 mmol/l ≈ 10·2 mg/100 ml. Ketone bodies: 1 mmol/l ≈ 10·4 mg/100 ml. Glycerol: 1 mmol/l ≈ 9·2 mg/100 ml.

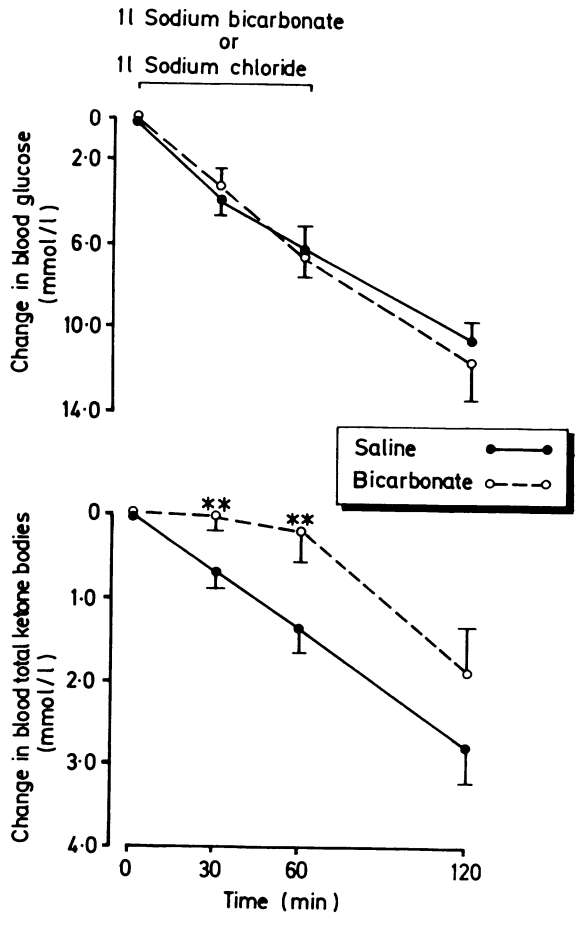

FIG 1—Change in blood glucose and blood total ketone body concentrations with infusion of 1 l sodium bicarbonate (150 mmol/l) or 1 l sodium chloride (150 mmol/l).
** Significant difference between the two groups ($p < 0·02$).
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. Ketone bodies: 1 mmol/l ≈ 10·4 mg/100 ml.

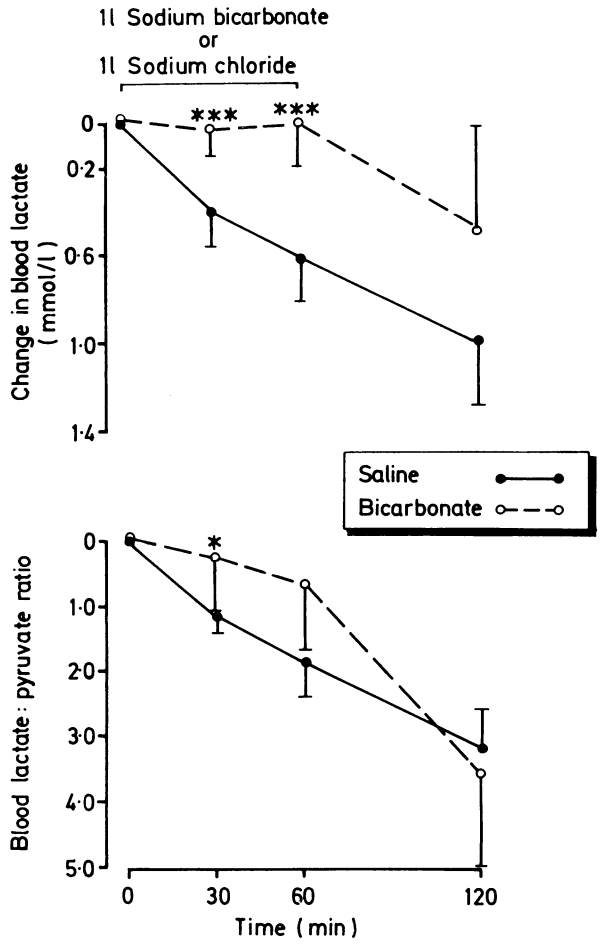

FIG 2—Change in blood lactate concentration and in blood lactate:pyruvate ratio with infusion of 1 l sodium bicarbonate (150 mmol/l) or 1 l sodium chloride (150 mmol/l).
***$p < 0·01$; *$p < 0·05$.
Conversion: SI to traditional units—Lactate: 1 mmol/l ≈ 9 mg/100 ml.

Blood glucose concentration at time zero was similar in the two groups (table), and they showed no significant difference in the fall in blood glucose concentration over 120 minutes (fig 1).

At time zero blood total ketone body concentrations were 12·1 (SEM 0·6) mmol/l (126 (6) mg/100 ml) and 12·6 (SEM 0·7) mmol/l (131 (7) mg/100 ml) in the bicarbonate and saline treated groups respectively. During infusion of bicarbonate there was no significant change in blood total ketone body concentration, but in patients not receiving bicarbonate there was a fall of 1·4 (SEM 0·3) mmol/l (15 (3) mg/100 ml). The difference in fall was significant ($p < 0·02$; fig 1). From 60 to 120 minutes the fall was similar in both groups (1·6 (SEM 0·5) mmol/l (17 (5) mg/100 ml) in the bicarbonate group and 1·4 (SEM 0·4) mmol/l (15 (4) mg/100 ml) in the saline group).

From 0 to 60 minutes in the saline group the blood lactate concentrations fell by 0·62 (SEM 0·20) mmol/l (5·6 (1·8) mg/100 ml) but was unchanged in the bicarbonate group. The changes were significantly different ($p < 0·01$). From 60 to 120 minutes the two groups showed similar falls in blood lactate concentration (fig 2). The lactate:pyruvate ratio was not significantly different between the two groups at time zero (table). With bicarbonate infusion the fall was less than in the saline treated group (fig 2). The difference was significant at 30 minutes ($p < 0·02$).

Patterns of response of blood pyruvate, glycerol, and alanine concentrations (fig 3) were similar in the two groups and no significant differences were observed.

In the most severely acidotic patients (pH <7·05), of whom nine received saline and eight bicarbonate, blood glucose concentration fell at a similar rate irrespective of treatment and at the same rate as in patients with pH >7·05. Bicarbonate infusion delayed the fall in concentrations of lactate ($p < 0·02$ at 30 minutes; $p < 0·05$ at 60 minutes), total ketone bodies ($p < 0·05$ at 30 minutes; $p < 0·02$ at 60 minutes), and pyruvate ($p < 0·02$ at 60 minutes). The changes in lactate:pyruvate ratio did not differ significantly but the fall was quantitatively less in patients who received bicarbonate (0·3 (SEM 1·5) *v* 1·2 (0·3) at 30 minutes; 1·0 (1·8) *v* 2·1 (0·7) at 60 minutes).

Discussion

Infusion of bicarbonate in patients with diabetic ketoacidosis did not alter the rate of fall of blood glucose concentration as compared with saline over the study period. This is consistent with a previous report in man,[7] although acidosis has been implicated in causing insulin resistance in experimental acidosis in animals.[18 19]

Blood lactate concentration was raised (>1·2 mmol/l; >10·8 mg/100 ml) in 29 of our 32 patients with ketoacidosis at the start of the study and was greater than 5 mmol/l (45 mg/100 ml) in five. Lactic acidosis is defined as a metabolic acidosis with blood lactate concentration >5 mmol/l,[20] and probably in these patients lactic acidosis made an important contribution to the metabolic acidosis. Similar findings have been reported,[21] but it should be emphasised that in all patients except one the concentration of blood total ketone bodies was greater than that of lactate and hence made the predominant contribution. This distinction between lactic acidosis alone and hyperlactataemia accompanying ketoacidosis is important, since lactate concentration fell during the study in all patients with treatment of ketoacidosis and in no patient did lactic acidosis replace ketoacidosis during treatment.[22]

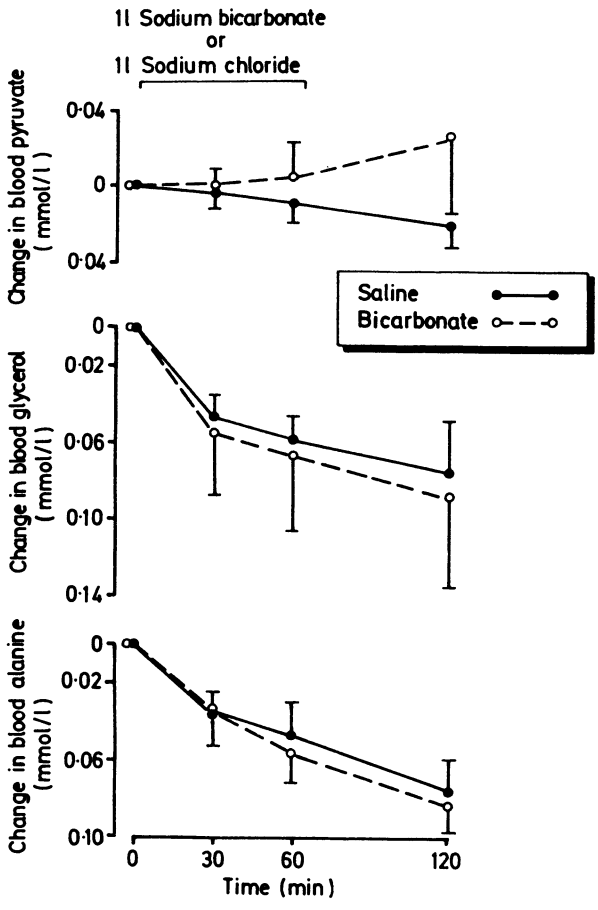

FIG 3—Change in blood pyruvate, glycerol, and alanine concentrations with infusion of 1 l sodium bicarbonate (150 mmol/l) or 1 l sodium chloride (150 mmol/l).

Conversion: SI to traditional units—Pyruvate: 1 mmol/l ≈ 8·8 mg/100 ml. Glycerol: 1 mmol/l ≈ 9·2 mg/100 ml. Alanine: 1 mmol/l ≈ 8·9 mg/100 ml.

We did observe, however, delay in the fall in blood lactate concentration and the lactate:pyruvate ratio in patients infused with bicarbonate. The equilibrium of the lactate-pyruvate reaction is influenced by acidosis such that both the lactate concentration and the lactate:pyruvate ratio are increased. In the saline treated group the rise in pH at 120 minutes was accompanied by a fall in lactate and the lactate:pyruvate ratio, but the greater rise in pH in patients given bicarbonate did not produce a greater fall in lactate or the lactate:pyruvate ratio. That this did not occur might suggest impaired intracellular pH correction or tissue hypoxia, though we share with other workers concern over extrapolation from blood to intracellular pH[23 24] and from blood lactate:pyruvate ratios to tissue lactate:pyruvate ratios,[25] which are considered to reflect the cytosolic ratio of reduced nicotinamide adenine dinucleotide to the oxidised form of this product. Nevertheless, the delayed fall in lactate and lactate:pyruvate ratio in patients given bicarbonate is consistent with the effects of tissue hypoxia.

Interestingly, significant differences in response were not observed for the 3-hydroxybutyrate:acetoacetate ratio, which reflects the mitochondrial redox state. Although this ratio increased in both groups at the start of the study, similar falls were observed. Knowledge of intramitochondrial pH and its relation to cytosolic pH and extracellular pH is limited, though differences in the pH of intracellular organelles is well recognised.[26]

The fall in blood total ketone bodies was significantly less in patients who received bicarbonate. The fall in ketone bodies which results from insulin administration is assumed to be due mainly to inhibition of lipolysis and hence decreased supply of non-esterified fatty acids to the liver, though the fate of fatty acids within the liver may be modified by changes in stress hormones which occur once treatment is started.[27] Following decreased ketogenesis the fall in blood total ketone bodies is due to clearance. Our results suggest that bicarbonate may modify changes in ketogenesis produced by insulin or impair clearance. An effect on lipolysis was not supported by the findings in blood glycerol concentration when similar falls were seen in both groups, though blood glycerol concentrations reflect hepatic uptake of glycerol in addition to peripheral production. Clearance of ketone bodies depends on tissue oxidation and renal excretion with an important contribution from respiratory excretion in ketoacidosis. Possibly the greater increase in pH in patients who received bicarbonate altered renal excretion of ketone bodies.

No differences in response between the two groups were observed for pyruvate and alanine concentrations. Interestingly, alanine concentrations fell steadily in both groups of patients. An inverse relation has been reported for alanine and total ketone bodies[28] which was not present in our patients. This relation may be modified by insulin administration, and the role of acidosis in the relation has received careful scrutiny.[29]

We conclude that the administration of bicarbonate for diabetic ketoacidosis, while not affecting the fall in blood glucose concentration, delays the improvement in concentrations of lactate and total ketone bodies and in the lactate:pyruvate ratio which is observed during treatment with saline and insulin. In part these findings are consistent with bicarbonate enhancing tissue hypoxia. There is therefore no metabolic indication for the use of intravenous bicarbonate in the treatment of diabetic ketoacidosis.

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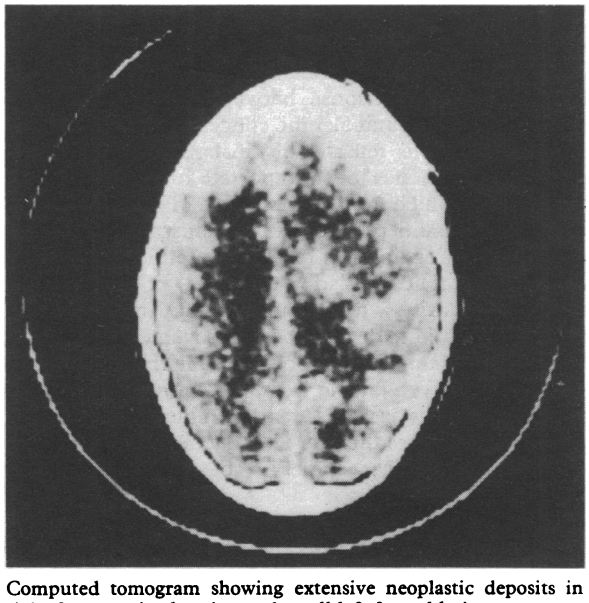
SHORT REPORTS

Cerebral glioma after cranial prophylaxis for acute lymphoblastic leukaemia

Intracranial sarcomas, meningiomas, and, more rarely, gliomas have been reported after cranial irradiation for unrelated conditions, with latent periods of many years.[1] We report on a child who developed a diffuse glioma nine years after successful treatment for acute lymphoblastic leukaemia.



Computed tomogram showing extensive neoplastic deposits in right frontoparietal region and small left frontal lesion.

Case report

A 3 year old girl presented in September 1974 with pallor, limb pain, cervical adenopathy, and hepatosplenomegaly. Initial haemoglobin concentration was 5·3 g/dl, white cell count $2{\cdot}4\times10^9$/l with 11% blast cells, and platelet count 26×10^9/l. Examination of marrow aspirate confirmed a diagnosis of acute lymphoblastic anaemia. She was treated according to the Medical Research Council UKALL III protocol, and remission was achieved by week 4. Prophylactic treatment of the central nervous system consisted of five weekly intrathecal injections of methotrexate 10 mg/m^2 body surface area and cranial irradiation using a 4 MeV linear accelerator with two opposed fields of 12×19 cm. The total dose was 24 Gy (2400 rad) delivered over 19 days in 12 fractions. Maintenance chemotherapy with mercaptopurine daily, methotrexate weekly, and vincristine and prednisolone every four weeks was continued until October 1977.

She remained well until December 1983, when she complained of frontal headaches and nausea for one month. There were no clinical or haematological abnormalities. On review 12 days later the headaches were worse and she had developed weakness of the left arm.

Examination showed a short attention span, bilateral papilloedema, left facial weakness, monoparesis of the left arm, cortical sensory loss, dyspraxia, dysmetria, mild dysdiadochokinesia, and a left Babinski's sign. She was treated with dexamethasone. A computed tomogram (figure) showed extensive neoplastic deposits in the right frontoparietal region and a small left frontal lesion. Marrow aspirate showed no sign of recurrence of leukaemia. Right frontal craniotomy and a frozen section of the mass showed a malignant glioma. Right anterior lobectomy with incomplete removal of the tumour was performed. Twelve hours after operation her condition deteriorated and she rapidly lost consciousness. A repeat scan showed right cerebral oedema. Intensive resuscitation failed, and she died three hours later. At necropsy there was pronounced cerebral oedema with early uncal herniation, and an astrocytoma was confirmed by histological examination.

Comment

Certain criteria must be met to sustain a diagnosis of neoplasia induced by radiation. The tumour must occur within the irradiated field and after a latent period sufficient to exclude its having been present at the time of radiotherapy. The tumour should differ histologically from the original lesion, and neurocutaneous syndromes predisposing to malignancy must be excluded. Primary conditions treated with radiation that have subsequently been associated with neoplasia have ranged from tinea capitis to pituitary adenomas[2] and medulloblastomas,[3] and the radiation dosage has ranged from 1·4 to 60 Gy (140 to 6000 rad). The latent period has usually exceeded five years.

Cure rates for acute lymphoblastic leukaemia in childhood have dramatically improved since the introduction of effective prophylactic treatment of the central nervous system with intrathecal methotrexate and cranial irradiation. The relative contributions of each to the subsequent development of a cerebral tumour cannot be assessed, but current trends have led to the reduction of radiation dosage from 24 to 18 Gy (2400 to 1800 rad) for all risk categories.

Two other cases of glioma after treatment of acute lymphoblastic leukaemia have been reported.[4,5] With the long latency of cerebral tumours related to treatment new cases may come to light, and continued close surveillance of patients after treatment is mandatory. It is essential to report new cases so that the incidence of this delayed complication can be assessed and possible risk features identified. Further modification of prophylactic treatment of the central nervous system may be possible, especially in patients at low risk, without affecting long term survival.

We thank Mr A J W Steers, consultant neurosurgeon, for his help in managing this patient.

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