than others to choose oversubscribed specialties in which such difficulties would have been expected. It is unlikely that graduates from ethnic minorities were less well qualified than their native European counterparts as there is no evidence that medical school admission policies discriminate in favour of less able applicants from ethnic minorities, and there is considerable evidence that the opposite is the case.^{1,3,7} The strength and consistency of the associations found in this study leave little doubt that discrimination against British trained doctors of ethnic minority origin occurs in the competition for training posts.

Most of this discrimination seems to have occurred in the process of shortlisting applicants for senior house officer and registrar posts. Differences between native European and ethnic minority graduates in success rates at interview were much less clear cut. Discrimination at the shortlisting stage may have been based on non-European names, country of birth, and other clues to ethnic origin. The filling of posts by personal arrangement rather than open competition is another possible mechanism of discrimination. Implementing a formal system of grading applicants for senior house officer and registrar posts might help to ensure fair treatment. Monitoring the ethnic mix of

doctors appointed in hospitals might also be useful in identifying sites where discrimination may be occurring. We understand that the Department of Health is preparing a draft circular on the implementation of equal opportunities in recruitment and selection procedures for hospital doctors.

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Serial prothrombin time as prognostic indicator in paracetamol induced fulminant hepatic failure

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Abstract

Objective—To find out whether changes in the daily prothrombin time are of prognostic importance in patients with paracetamol induced fulminant hepatic failure.

Design—Retrospective study.

Setting—The Liver Unit, King's College Hospital, London.

Patients—150 Consecutive patients with paracetamol induced fulminant hepatic failure admitted between October 1986 and February 1989.

Main outcome measure—Death.

Results—Of the 150 patients, 72 (48%) died. In all, 34 of the 37 (92%) patients with a peak prothrombin time of ≥ 180 seconds died as did 20 of the 41 (49%) with a time of 130-179 seconds, nine of the 25 (36%) with a time of 90-129 seconds, and nine of the 47 (19%) with a time of < 90 seconds. Of the 42 patients with a continuing rise in prothrombin time between days 3 and 4 after overdose, 39 died (93%) compared with 21 of the 96 (22%) in whom the prothrombin time fell.

Conclusions—These data indicate that a continued increase in prothrombin time on day 4 after overdose and a peak prothrombin time of ≥ 180 seconds identify at an early stage those patients with a less than 8% chance of survival. Liver transplantation should be considered in patients meeting either of these criteria.

Introduction

Survival rates in patients with paracetamol induced fulminant hepatic failure have improved in recent years, probably as a consequence of improvements in intensive liver care, though mortality still remains high (47% in our unit).¹ Many variables have been used to assess outcome in these patients,² and coagulation

studies have been established as prognostic indicators.³ In an early study in our unit factor VII concentration was shown to provide a good indication of prognosis,⁴ and, later use of serial factor VII concentrations were shown to improve the predictive power of this test.⁵ Bernuau *et al* in Paris, using multivariate analysis, found that a reduced factor V concentration was the most sensitive prognostic indicator in patients with fulminant hepatitis B infection.⁶ Assay of individual clotting factors is not, however, a routine investigation in most laboratories, whereas measurement of the prothrombin time is reproducible and nearly always available. In a recent analysis of data we showed that a peak prothrombin time of > 100 seconds provided prognostic information in patients with paracetamol induced fulminant hepatic failure, though supplementary information (that is, serum creatinine concentration and grade of coma) was required to identify patients who had a particularly poor outcome.⁷

The urgency to define the likely outcome as early as possible after the overdose has been increased by the availability of liver transplantation, which is increasingly utilised in patients with fulminant hepatic failure of other aetiologies.⁸⁻¹² In this study we reviewed a series of 150 consecutive patients with paracetamol induced fulminant hepatic failure to investigate whether changes in the daily prothrombin time complemented the peak prothrombin time in identifying a high risk group who would benefit from liver transplantation.

Patients and methods

In all, 150 patients with paracetamol induced fulminant hepatic failure were treated in the liver failure unit between October 1986 and February 1989. All of them met the criteria of Trey and Davidson for the diagnosis of fulminant hepatic failure.¹³ Most patients

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are admitted to the liver failure unit from the referring hospitals on the second or third days after drug ingestion because: (1) they are becoming encephalopathic; (2) they have a rapidly progressing coagulopathy; (3) they are acidotic; or (4) they have renal failure. Ninety four of the patients were women with a mean age of 29.8 years (range 14-62). The 56 men had a mean age of 34.1 years (range 13-62). One man underwent successful orthotopic liver transplantation during the study period. He had been selected on the basis that his prognosis was very poor, and for the purposes of the statistical analysis he was assigned to the group of patients who died.

The morning prothrombin time for each patient was recorded, along with whether it was rising or falling, in relation to the number of days since the overdose and the final outcome. Day 1 was defined as the day after that on which the overdose occurred. The prothrombin times were measured in seconds against a standard control time of 15 seconds. If the specimen had not coagulated by 180 seconds the reaction was not continued and a time of ≥ 180 seconds was recorded. Patients were allocated to one of four groups according to whether their peak prothrombin time was <90 , 90-129, 130-179, or ≥ 180 seconds.

The peak prothrombin times and the changes in prothrombin times between days after overdose were analysed in relation to patient outcome using the χ^2 test with Yates's correction. The ability for any chosen variable to predict accurately the prognosis was assessed by using positive predictive value, specificity, sensitivity, and predictive accuracy. Positive predictive value was defined as the mortality in those predicted to have a poor prognosis. Specificity was defined as the ratio of the number of survivors correctly predicted by the test to the actual number of survivors, sensitivity as the number of patients accurately predicted to die divided by the total number of those who died, and predictive accuracy as the number of patients whose outcome was predicted correctly divided by the total number of patients.

Results

The overall mortality in this cohort was 48% (72/150). No patients died on day 1 after the overdose, but mortality on days 2-8 was 3% (5/150), 5% (7/145), 19% (26/138), 12% (13/112), 5% (5/99), 6% (6/94), and 3% (3/88), respectively, and after day 8 it was 8% (7/85).

The peak prothrombin time was an indicator of eventual outcome (table I). Table II gives the relation between changes in the morning prothrombin time on consecutive days and eventual outcome. All patients had a rise in morning prothrombin time on day 1 after the overdose and most of them had a continuing rise up to and including day 3, which did not predict the eventual outcome. In contrast, a continuing rise in the morning prothrombin time between days 3 and 4 was associated with a particularly poor prognosis: mortality was 93% (39/42) compared with 22% (21/96) if the prothrombin time fell between these two days ($p<0.001$). All patients with an increase in prothrombin

time on any day after day 4 died independent of whether this was a continuing rise or a rise after a previous fall. There were only four patients in whom the prothrombin time beyond day 4 rose after a fall, and the rise was associated with sepsis in all cases. In most of the patients, whatever their outcome, the prothrombin time fell on or after day 5. There were 10 patients whose prothrombin time fell on day 3 after the overdose and who still died: five died early, one died on day 3, and four died on day 4; the other five developed late sepsis after making an initial recovery, one dying on day 7 and two on days 11 and 10. The three patients who survived despite having a continued

TABLE II—Outcome with relation to changes in the morning prothrombin time in 150 patients with paracetamol induced fulminant hepatic failure

No of days after paracetamol overdose	Change in prothrombin time	Outcome*	
		No (%) who survived	No (%) who died
1	Rise (n=150)	78 (52)	72 (48)
2	Continuing rise (n=147)	75 (51)	72 (49)
	Fall (n=3)	3 (100)	
3	Continuing rise (n=114)	57 (50)	57 (50)
	Fall (n=31)	21 (68)	10 (32)
4	Continuing rise† (n=42)	3 (7)	39 (93)
	Fall (n=96)	75 (78)	21 (22)
5	Continuing rise (n=11)		11 (100)
	Fall (n=101)	78 (77)	23 (23)
6	Rise‡ (n=3)		3 (100)
	Fall (n=96)	78 (81)	18 (19)
≥ 7	Rise‡ (n=5)		5 (100)

*Eventual outcome rather than outcome on that day.

† $p<0.001$ Compared with a fall in prothrombin time on day 4; χ^2 test with Yates's correction.

‡A continuing rise or rise after a fall in prothrombin time.

rise in prothrombin time on day 4 all had a substantial rise but their peak prothrombin time was <180 seconds.

Both a continuing rise in prothrombin time on day 4 after overdose and a peak prothrombin time of ≥ 180 seconds have a specificity of 0.96 as prognostic indicators. Although the continuing rise is a more sensitive index of poor outcome (sensitivity 0.54 compared with 0.47), they have similar positive predictive values (0.93 and 0.92 respectively) (table III).

TABLE III—Assessment of peak prothrombin time and change in prothrombin time as prognostic indicators in 150 patients with paracetamol induced fulminant hepatic failure

	Positive predictive value	Sensitivity	Specificity	Predictive accuracy
Continuing rise in prothrombin time on day 4 (n=42)	0.93	0.54	0.96	0.75
Peak prothrombin time ≥ 180 s (n=37)	0.92	0.47	0.96	0.73
Peak prothrombin time ≥ 180 s and continuing rise in prothrombin time on day 4 (n=25)	1.00	0.35	1.00	0.69
Peak prothrombin time ≥ 180 s or continuing rise in prothrombin time on day 4 (n=53)	0.89	0.65	0.92	0.79

The specificity and positive predictive value are increased to 1.00 if a single criterion of a prothrombin time rising on day 4 after overdose and peaking at ≥ 180 seconds is taken to predict death, but only at the expense of a fall in sensitivity to 0.35 and predictive accuracy to 0.69.

Discussion

The prothrombin time is a measure of the extrinsic pathway of coagulation and quantifies the activity of coagulation factors VII, V, and X, along with their ability to produce fibrin from fibrinogen through the

TABLE I—Outcome with relation to peak prothrombin time in 150 patients with paracetamol induced fulminant hepatic failure

Peak prothrombin time (s)	Outcome	
	No (%) who survived	No (%) who died
$\geq 180^*$ (n=37)	3 (8)	34 (92)
130-179 (n=41)	21 (51)	20 (49)
90-129 (n=25)	16 (64)	9 (36)
<90 (n=47)	38 (81)	9 (19)
Total (n=150)	78 (52)	72 (48)

* $p<0.001$; χ^2 Test with Yates's correction.

action of thrombin. As some of the coagulation factors have short half lives—for example, factor VII has a half life of only two to five hours—the prothrombin time is a good marker of the synthetic capacity of the liver and hence reflects the severity of hepatic necrosis. The observation that the prothrombin time peaks on the third day after paracetamol overdose in those patients who are going to survive and on the fourth day or later in those who will not presumably reflects either a greater degree of hepatic necrosis or a delay in hepatocyte regeneration in those patients who die. This study has shown that monitoring the daily changes in the prothrombin time in patients with paracetamol induced fulminant hepatic failure can identify a high risk group who could benefit from orthotopic liver transplantation.

An increase in prothrombin time on day 4 after overdose and a peak prothrombin time of ≥ 180 seconds can identify 65% of the patients with a fatal outcome. Both have been found to be specific indicators of a poor prognosis with high positive predictive values. Only acidosis on admission (pH < 7.3), as described in our unit,⁷ has been found to be a more discriminating variable (specificity 0.99 and positive predictive value 0.95) than either of the two indicators reported here if applied individually. In those patients with early acidosis the decision to proceed with transplantation has to be taken quickly due to the rapidity of deterioration. To our knowledge there are no reports of a prognostic indicator that is more discerning than the two we report here when used in combination. When choosing patients with paracetamol induced fulminant hepatic failure for liver transplantation it is necessary to utilise prognostic indicators that have high positive predictive values to reduce the incidence of inappropriate transplantation as the patients who recover without transplantation do so completely.

Only 12% of patients with a fatal outcome die during the first three days after the overdose. Therefore, using the criteria identified in this study, the prognosis of the remaining patients can be evaluated to a high degree of certainty on or before the morning of the fourth day after overdose and, consequently, soon after admission to the unit. This allows sufficient time to locate a donor and perform liver transplantation before the onset of complications such as cerebral oedema, hypotension, and infection, which add to the hazards of the procedure. Also, the criteria do not rely on deep coma to predict a fatal outcome.

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Recurrent rupture of intracranial aneurysms in autosomal dominant polycystic kidney disease

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The prevalence of intracranial aneurysms is increased in autosomal dominant polycystic kidney disease. Rupture of such aneurysms is one of the most serious complications of the disease. Decision analysis performed by Levey *et al* indicated that routine screening with cerebral arteriography was not warranted in patients with the disease.¹ In the analysis Levey *et al* assumed that patients who survive surgery following rupture of an aneurysm are not at risk of recurrent rupture of that aneurysm. They suggested, however, that "new aneurysms may occur and rupture," but to our knowledge this has not been shown. We report the recurrent development and rupture of intracranial aneurysms in three unrelated patients with autosomal dominant polycystic kidney disease.

Case reports

The table gives clinical data on the three patients.

Case 1—A 20 year old normotensive woman was referred with a subarachnoid haemorrhage. Cerebral arteriography showed an aneurysm of the right middle

cerebral artery, which was clipped. Five years later autosomal dominant polycystic kidney disease was diagnosed by renal ultrasonography and from her family history: her mother and a brother and his two sons were affected but did not have a history of symptomatic intracranial aneurysm or severe renal failure. At the age of 34 she suddenly became comatose with a right hemiplegia. Cerebral arteriography showed an aneurysm of the posterior communicating artery, which was clipped. Aphasia persisted.

Case 2—A 22 year old woman was admitted with a subarachnoid haemorrhage. Autosomal dominant polycystic kidney disease had been diagnosed when she was 8 by intravenous pyelography and from her family history: her brother and father were both affected. Her brother required regular haemodialysis from the age of 35 and her father died suddenly of a stroke when he was 50. On admission cerebral arteriography showed an aneurysm of the right internal carotid artery, which was clipped. The patient remained well, and repeat angiography yielded normal results. One year later she developed arterial hypertension, which was controlled by a β blocker. Subsequently she developed progressive renal failure. At the age of 32 she was readmitted with a subarachnoid haemorrhage. Four vessel angiography showed three aneurysms (two anterior, one posterior) on the right side of the circle of Willis; all were clipped. A left hemiparesis persisted postoperatively. Haemodialysis was started three years later.

Case 3—A 29 year old man was admitted with a subarachnoid haemorrhage. Autosomal dominant polycystic kidney disease had been diagnosed two months previously on the basis of untreated hypertension, moderate renal failure, and bilateral cysts on ultrasonography. His mother, a brother, and a sister

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