improved postnatal growth. This may help to reduce the high infant mortality suffered by Asian groups.

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Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic

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Abstract

***Objective*—To determine the cause of a large increase in the number of children with unexplained renal failure.**

***Design*—Case-control study.**

***Setting*—Children's hospital in Dhaka, Bangladesh.**

***Subjects*—Cases were all 339 children with initially unexplained renal failure; controls were 90 children with cause of renal failure identified; all were admitted to hospital during 35 months after January 1990.**

***Main outcome measures*—Differences between the case and control patients in clinical and histological features and outcome; toxicological examination of 69 bottles of paracetamol from patients and pharmacies.**

***Results*—Compared with children with an identified cause for their renal failure, children with initially unexplained renal failure were significantly ($P<0.05$) more likely to have hepatomegaly (58% *v* 33%), oedema (37% *v* 20%), and hypertension (58% *v* 23%); to have a higher serum creatinine concentration (mean 519 μmol/l *v* 347 μmol/l) and lower serum bicarbonate concentration (10·1 mmol/l *v* 12·4 mmol/l); to have been given a drug for fever (91% *v* 31%); to have ingested a brand of paracetamol shown to contain diethylene glycol (20% *v* 0%); and to have died in hospital (70% *v* 33%). Diethylene glycol was identified in 19 bottles of paracetamol, from 7 of 28 brands tested. In the 12 months after a government ban on the sale of paracetamol elixir, new cases of renal failure decreased by 54%, and cases of unexplained renal failure decreased by 84%.**

***Conclusion*—Paracetamol elixirs with diethylene glycol as a diluent were responsible for a large outbreak of fatal renal failure in Bangladesh.**

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Introduction

Diethylene glycol is a highly toxic organic solvent that causes acute renal failure and death when ingested.[1-3] Its toxicity became apparent when in the 1930s it was used to prepare a sulphanilamide elixir in the United States.[3] The deaths of at least 76 people from ingestion of this sulphanilamide elixir prompted the passage of the United States Food, Drugs, and Cosmetics Act in 1938, which regulates the evaluation and use of new drugs or foods.[4]

Diethylene glycol is still occasionally identified in medical preparations or foods, though rarely in lethal concentrations.[5-12] This report presents the results of investigations carried out in response to a large, initially unexplained epidemic of acute renal failure that was due to diethylene glycol poisoning.

Methods

PATIENTS

This study was conducted by Dhaka Shishu Hospital, the major children's hospital in the capital of Bangladesh. A dramatic increase in the number of patients with unexplained renal failure was noted in October 1990. Beginning in November 1990 possible causes for this increase were sought. Case records of patients admitted with renal failure from January 1990 onwards were reviewed, and information on all newly diagnosed patients with renal failure was recorded. Information obtained from patients' charts included history and physical examination findings and the results of complete blood counts, serum electrolye and creatinine concentrations, and blood culture, if performed. Nutritional status was assessed with standard criteria.[13] Hypertension was defined as mean arterial blood pressure above the 95th centile for age.[14]

Because toxin ingestion was suspected as the cause of the epidemic of renal failure, special attention was paid to identifying medicines taken before renal failure developed. This was done by questioning the child's parents and asking them to bring to the hospital for verification any medicines given to the child.

The most commonly identified causes of acute renal failure at Shishu Hospital are the haemolytic-uraemic syndrome, poststreptococcal glomerulonephritis, and acute tubular necrosis. All three conditions are usually readily diagnosed on the basis of history, physical examination, and laboratory findings. Patients in whom the cause of renal failure was not identified were considered to have unexplained renal failure.

TESTING OF SAMPLES

Paracetamol elixir was identified as the medicine most commonly taken before admission by patients developing unexplained renal failure. Samples tested by laboratories in Bangladesh did not identify the presence of toxic substances, so 69 samples of 28 brands of paracetamol were submitted on four occasions for analysis to the State Laboratory Institute of the Commonwealth of Massachusetts in Boston. Samples for analysis included three bottles from the stocks of the hospital pharmacy, 49 bottles purchased

without prescription by members of the study team from 10 pharmacies in the Dhaka area, and 17 bottles obtained from patients with unexplained renal failure. These samples were transported to Boston for analysis by gas chromatography and mass spectrometry.

STATISTICAL METHODS

Data were entered into a personal computer using Statpac Gold version 3.0 (Walonick Associates, Minneapolis, MN) and analysed with SPSS version 6.0 for Windows (SPSS Incorporated, Chicago, IL) and EpiInfo version 5.01a (USD Incorporated, Stone Mountain, GA). The significance of differences in proportions was tested with the χ^2 test or Fisher's exact test if the predicted size of any cell was five or less. Exact confidence intervals for odds ratios were used. Differences between the means of more than two groups were tested for significance by using a one way analysis of variance, or the Kruskal-Wallis test if the observations were not normally distributed. If the overall difference between groups was significant, differences between individual groups were tested by using Student's *t* tests or the Wilcoxon rank sum test. For multiple comparisons the Bonferroni adjustment of significance level was used. Tests of significance were two tailed. All laboratory variables that were age dependent were adjusted for age and compared by using analysis of covariance.

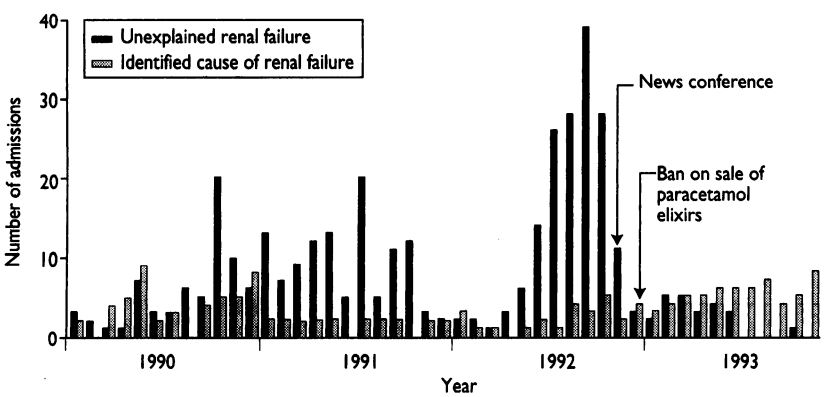
TABLE I—*Characteristics of 429 children with acute renal failure admitted to Dhaka Shishu Hospital between 1 January 1990 and 1 December 1992. Values are numbers (percentages) unless stated otherwise*

Characteristic	Unexplained renal failure (n=339)	Cause of renal failure identified (n=90)	P value
Median (range) age (months)	24 (1-144)	13 (1-152)	<0·001
Boys	235 (69·3)	64 (71·1)	0·842
Nutritional status*:			
Mild or no malnutrition	220 (69)	50 (62)	0·267
Moderate malnutrition	67 (21)	16 (20)	0·925
Severe malnutrition	32 (10)	15 (19)	0·054
Clinical features:			
Hepatomegaly	195 (58)	30 (33)	<0·001
Oedema	126 (37)	18 (20)	0·003
Hypertension†	197 (58)	21 (23)	<0·001
Laboratory investigations:			
Mean (SD) creatinine (μmol/l)	519 (202)	347 (178)	<0·001
Mean (SD) sodium (mmol/l)	130 (7)	130 (12)	0·858
Mean (SD) potassium (mmol/l)	4·7 (1·3)	4·4 (1·5)	0·120
Mean (SD) bicarbonate (mmol/l)	10·1 (3·5)	12·4 (4·7)	0·010
Mean (SD) haemoglobin (g/l)	86 (17)	74 (26)	<0·001
Mean (SD) blood leucocyte count (×10⁹/l)	13·7 (5·9)	23·4 (16)	<0·001

*Determined using National Centre for Health Statistics standards.[13] Moderate=weight for age >35 D below median for age; severe=weight for age >45D below median for age. Unexplained renal failure, n=319; cause identified, n=81. Overall P=0·105.
†Mean arterial blood pressure above 95th centile for age.[14]

TABLE II—*Paracetamol ingestion in 429 children admitted to Dhaka Shishu Hospital with acute renal failure between 1 January 1990 and 1 December 1992*

Medicine ingested	No (%) with unexplained renal failure (n=339)	No (%) with cause of renal failure identified (n=90)	Odds ratio (95% confidence interval)	P value
Any medicine for fever	308 (91)	28 (31)	22·0 (12·3 to 39·3)	<0·001
Any paracetamol	99 (29)	2 (2)	18·2 (4·4 to 75·2)	<0·001
Paracetamol of brand found to contain diethylene glycol	67 (20)	0	∞	<0·001



Admissions for acute renal failure to Dhaka Shishu Hospital, 1 January to 1 December 1993

Results

From 1 January 1990 to 1 December 1992, 429 patients with acute renal failure were admitted to the renal unit. The cause of renal failure was identified in 90 (21%): 40 (44%) had the haemolytic-uraemic syndrome, 49 (55%) had acute tubular necrosis following severe dehydration or shock, and 1 (1%) had poststreptococcal glomerulonephritis. The cause of renal failure in the remaining 339 (79%) patients could not be identified initially.

Patients without an identified cause for their renal failure were older, better nourished, and more often had hepatomegaly, generalised oedema, and hypertension (table I). They also had a higher mean serum creatinine (519 μmol/l *v* 347 μmol/l; P<0·001) and blood haemoglobin (86 g/l *v* 74 g/l; P<0·001) concentrations on admission to the dialysis unit, but a lower serum bicarbonate concentration (10·1 mmol/l *v* 12·4 mmol/l; P=0·010) and blood leucocyte count (13·7×10⁹/l *v* 23·4×10⁹/l; P<0·001).

When compared with the 90 patients with an identified cause for their renal failure, a significantly higher proportion of the 339 patients with no identified cause for renal failure had been given a medicine for fever (308 (91%) *v* 28 (31%); P<0·001) or an elixir known to be paracetamol (99 (29%) *v* 2 (2%); P<0·001). Of these 339 patients, 67 had taken a brand of elixir subsequently found to contain diethylene glycol; none of the 90 patients with an identified cause for their renal failure had done so (P< 0·001, odds ratio ∞) (table II). The clinical features of 272 children with unexplained renal failure in whom ingestion of one of these brands could not be documented were similar to those of these 67 children.

ANALYSIS OF PARACETAMOL ELIXIRS

Nineteen of 69 paracetamol elixirs tested, from seven of the 28 different brands evaluated, contained diethylene glycol. Diethylene glycol was the sole diluent found in these 19 elixirs. The remaining 50 elixirs all had propylene glycol or glycerol as the diluent. All but one of the 69 elixirs contained paracetamol in approximately the concentrations stated on the product label.

Three of the elixirs containing diethylene glycol were from the stock of the hospital's pharmacy, four were purchased at three different pharmacies, and 12 were from patients. Multiple bottles were tested from 19 of the 28 manufacturers; in three brands all bottles tested positive (including three different batches of one brand in which nine bottles contained diethylene glycol); in 15 brands all bottles tested negative; and in one brand bottles of paracetamol with and without diethylene glycol were found. Manufacturing dates were available for seven of the 19 bottles containing diethylene glycol and ranged from September 1990 to September 1992.

After diethylene glycol was found in these paracetamol elixirs the government of Bangladesh, with the assistance of the World Health Organisation, analysed 104 different brands of paracetamol elixir. In this survey five bands (all also identified in the Massachusetts testing) were found to contain diethylene glycol.[15,16]

PATTERN OF THE EPIDEMIC

From January 1990 to December 1992, a mean of 10 patients with unexplained renal failure were admitted monthly to the dialysis unit (figure). Between August

and October 1990, 25 children developed acute renal failure while undergoing treatment at Dhaka Shishu Hospital for other illnesses. All had received paracetamol elixir supplied by the hospital pharmacy. The brand of paracetamol used was later shown to contain diethylene glycol.

The government of Bangladesh banned the sale of paracetamol elixirs in December 1992. In the 12 months after the ban, total admissions for renal failure declined by 53% (from 187 to 89 patients) and admissions for unexplained renal failure declined by 84% (from 162 to 26 patients). In the last six months of 1993 only one patient with unexplained renal failure was admitted.

PATIENT OUTCOME

Patients with unexplained renal failure had an in hospital fatality rate of 70%, compared with 33% for patients with a known cause for their renal failure ($P < 0.001$, relative risk 2·09 (95% confidence interval 1·55 to 2·82); table III). Only two of the 67 patients known to have ingested a brand of paracetamol containing diethylene glycol were discharged from the hospital improved.

Discussion

This investigation of an epidemic of acute renal failure strongly implicates diethylene glycol in paracetamol elixirs as the cause of the epidemic. The 339 patients with unexplained renal failure were 13·3 times more likely to have ingested a paracetamol elixir than the 90 patients with a known cause for their renal failure, and a history of ingestion of a brand of paracetamol that contained diethylene glycol was found only in children with unexplained renal failure. The clinical features of patients with unexplained renal failure—hepatomegaly, acidosis, oedema, and a high fatality rate—are consistent with the features of diethylene glycol poisoning.[1-3] Withdrawal of paracetamol elixirs from the market resulted in a precipitous decline in the number of patients with unexplained renal failure.

OUTBREAKS

This outbreak of fatal diethylene glycol poisoning is one of the largest reported. Fifty one patients who died in this outbreak were documented to have ingested a brand of paracetamol shown to contain diethylene glycol, and the actual number of deaths was undoubtedly far greater. An additional 185 patients with unexplained renal failure died at Shishu Hospital during the study period; 85% had ingested an unknown elixir for fever. Though in these patients the elixirs consumed could not be obtained from the patient's families for identification and analysis, it is probable that many, if not most, were paracetamol elixirs containing diethylene glycol. Many children poisoned by diethylene glycol undoubtedly went to other medical facilities, died at home, or lived in rural areas, where the majority of Bangladesh's 120 million people live[17] and where the implicated brands of paracetamol were also sold.

Other reported episodes of diethylene glycol poisoning include the 1937 outbreak in the United States,[3] seven deaths of children in South Africa in 1969 associated with liquid sedatives,[5] 21 cases of renal impairment in the Netherlands in 1985 attributed to wine containing diethylene glycol,[6-8] and the deaths of 14 adults in India in 1986 associated with the use of glycerin.[10] The episode most closely resembling this outbreak is the death of 47 Nigerian children who also ingested paracetamol elixirs containing diethylene glycol.[12]

DRUG MANUFACTURE

The point in the manufacturing or distribution of the paracetamol elixirs at which the substitution of diethylene glycol for propylene glycol occurred is uncertain. Samples of paracetamol that tested positive for diethylene glycol were obtained from various sources, including the pharmacy of Dhaka Shishu Hospital, whose supply was purchased directly from the manufacturer. It is thus unlikely that the medicines were tampered with at the retail level. The pharmaceutical manufacturers may have knowingly substituted the less expensive diethylene glycol for propylene glycol. The presence of paracetamol in all but one of the 69 bottles of paracetamol, however, suggests that the manufacturers were not producing an entirely spurious product. Either the foreign manufacturers or distributors, or the local importers and distributors, of propylene glycol could have substituted diethylene glycol for the more expensive propylene glycol (neither is produced in Bangladesh). The Nigerian outbreak was attributed to wholesale distributors making this substitution when selling to small pharmaceutical manufacturers.[12]

MONITORING DRUG SUPPLY

That this outbreak of diethylene glycol poisoning occurred, and continued for at least 35 months, reflects the difficulties of monitoring the drug supply and of enforcing pharmaceutical legislation in a developing country such as Bangladesh. The Bangladesh Drug Administration has an annual budget of $250 000 and 134 staff members, of whom only 43 are assigned to inspection, licensing, and testing.[18] These 43 people have responsibility for licensing and monitoring 208 pharmaceutical companies, 4625 licensed drug preparations, 1208 wholesale drug distributors, and 19 873 licensed drug retailers.[11] The administration operates a drug testing laboratory, but maintaining quality control in the face of financial constraints, the limited supply of equipment and reagents, and political interference in staffing and functioning is difficult.[16 18-20] Doctors at Dhaka Shishu Hospital notified the administration in November 1990 of their concerns about the paracetamol elixirs. Samples of nine brands of paracetamol (two of which were subsequently found to contain diethylene glycol) were submitted from Shishu Hospital to the Bangladesh Drug Administration for testing in 1991, 1992, and 1993. No report on testing of the samples was received. Additional samples were submitted to two private laboratories in Bangladesh, which were unable to identify diethylene glycol. Government intervention occurred only after a press conference in November 1992 by doctors from Shishu Hospital announcing the results of the toxicological findings of the Massachusetts laboratory.

Efforts to monitor the drug supply for safety are complicated by the proliferation of manufacturers of

TABLE III—*Outcome in 429 children with acute renal failure admitted to Dhaka Shishu Hospital between 1 January 1990 and 1 December 1992. Values are numbers (percentages)*

	Unexplained renal failure		
	Group 1: history of ingestion of paracetamol brand containing diethylene glycol (n=67)	Group 2: no history of ingestion of brand of paracetamol containing diethylene glycol (n=272)	Group 3: identified cause of renal failure (n=90)
Discharged alive*	2 (3)	29 (11)	42 (47)
Died in hospital†	51 (76)	185 (68)	30 (33)
Discharged against medical advice‡	14 (21)	58 (21)	17 (19)

Overall $P < 0.001$.
*Groups 1 or 2 *v* group 3, $P = < 0.001$; group 1 *v* group 2, $P = 0.086$.
†Groups 1 or 2 *v* group 3, $P = < 0.001$; group 1 *v* group 2, $P = 0.250$. Relative risk of death (95% confidence interval): group 1 *v* group 2 = 1·12 (0·96 to 1·31); group 1 *v* group 3 = 2·28 (1·66 to 3·15); group 2 *v* group 3 = 2·04 (1·51 to 13·76); groups 1 and 2 *v* group 3 = 2·09 (1·55 to 2·82).
‡Group 1 *v* group 2, $P = 0.93$; group 2 *v* group 3, $P = 0.73$; group 1 *v* group 3, $P = 091$.

paracetamol. More than 100 different manufacturers were licensed to produce and market paracetamol elixirs at the time of this outbreak.[16] All seven of the eight manufacturers of brands of paracetamol found to contain diethylene glycol were small companies with little capacity for quality control which, together with 180 other small manufacturers, account for less than 10% of drug production in Bangladesh.[18] This proliferation of small pharmaceutical manufacturers is also occurring in other developing countries.[21]

Paracetamol is on the World Health Organisation's list of essential drugs[22] and is widely used in developing countries. The substitution of diethylene glycol for propylene glycol in paracetamol elixirs produced in two widely separated countries, Nigeria and Bangladesh, suggests that another such epidemic could happen elsewhere. The capacity of governments in developing countries to effectively monitor the importation, production, and sale of drugs will have to be improved if tragedies such as this are to be prevented.

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Changes in body weight and incidence of hip fracture among middle aged Norwegians

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Lean body stature is an important risk factor for hip fracture.[1] We assessed prospectively the relation between intrapersonal change in body weight and the incidence of hip fracture.

Subjects, methods, and results

We followed up 21 510 women and 21 157 men born between 1925 and 1940 attending both the first (1974-8) and the similar second (1977-83) cardiovascular screening in three Norwegian counties (85·2% of all invited)[2] on average 11·3 (range 0·01-13·8) years after the second screening to study the incidence of hip fracture. We identified hip fractures (cervical or trochanteric) as described elsewhere[1] at all hospitals in the three counties. We calculated the observation time for each person from the second screening to hip fracture, emigration, death, or end of follow up (in that order). We matched the file to the cancer registry of Norway, which has information on all diagnosed cancers in Norway, and to the register of death and emigration form "Statistics Norway." Adjustment was made for potential confounders as described in a previous study of this cohort.[1]

During follow up we identified 227 hip fractures, excluding fractures associated with high energy traumas and metastatic bone disease. The mean age at fracture was 57·2 (range 46·7-65·9) years in women and 55·5 (42·9-65·0) years in men.

The mean weight in the total cohort increased by 1·3 (SD 4·3) kg between the first and second screening. The women losing more than 3 kg (1 SD from mean change) or gaining $\geq$5·6 kg (1 SD from mean change) had a distinctly higher risk of hip fracture (table). The same pattern, although not significant for those gaining $\geq$5·6 kg, was found in the men. Excluding all the subjects in whom cancer had ever been diagnosed and all those who died during follow up gave only minor changes in the relative risks. The same applied to additional adjustment for changes in physical activity and smoking habits between the first and second screening. If the whole study population had been exposed to the age adjusted rates of those gaining only 1·3-5·5 kg in weight then the incidence of hip fracture would have been reduced by 35% in the women and 26% in the men.

Comment

We found that both weight loss and excess weight gain, calculated from standardised weight measurements at two screenings of the same population, were strong predictors of hip fracture. This was in addition to body mass index, which is also a strong predictor of fracture.[1]

A relation between weight loss and hip fracture has previously been shown, and weight and bone loss is also associated with bone loss.[4] The raised risk of fracture in the