Hospital Topics

Deaths of two hospital inpatients poisoned by pilocarpine

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Abstract

Two inpatients of one hospital ward died. Pilocarpine poisoning was suspected and subsequently confirmed by analysis of urine. The circumstantial evidence strongly suggested that the food given to the patients in the ward had been adulterated. Police inquiries failed to elicit any further information, and open verdicts were returned at the inquest. Precautions taken subsequently to prevent a similar event—sealing food containers and trolleys—entailed a capital cost of £43 000. In addition, food stores were kept locked and tighter control kept on drugs stored in ward pharmacies.

Introduction

West Park Hospital is a long stay psychiatric unit on a large campus. About 40 minutes after the evening meal of soup and cottage pie on 14 August 1985 in Exford ward, which has 24 female psychogeriatric patients, most of the patients experienced a bout of coughing together with salivation, and some were cyanosed. Five of the patients became dyspnoeic; two recovered quickly, but three

deteriorated and were transferred to Epsom District Hospital after oral suction and oxygen treatment. One of these three improved and was transferred back to West Park Hospital after two days, the two others died.

The food had been prepared in the central kitchens and had been transported to many wards, but the symptoms described were peculiar to patients in Exford ward. Nevertheless, the catering manager inspected the kitchens for contamination. Environmental health officers, the medical officer for environmental health (HG), senior nurses, pharmacists, and administrators made extensive inquiries to no avail. Reluctantly they concluded that the food for that particular ward had been adulterated, and the police were informed the next day.

Clinical course of illness while patients were at Epsom District Hospital

CLINICAL DETAILS OF PATIENTS ON ARRIVAL

Case 1—This 86 year old woman, who was confused but alert, was taking bendrofluazide 5 mg daily for hypertension. She was dyspnoeic at rest but not cyanosed, with a pulse rate of 90 beats/min and blood pressure of 120/80 mm Hg. Auscultation of her chest showed a few rhonchi and crepitations. A chest x ray film was clear. Further investigations showed a haemoglobin concentration of 118 g/l, white cell count $12.6 \times 10^9/l$, and normal urea and electrolyte concentrations.

Case 2—This 82 year old woman was alert but confused and aggressive (her usual mental state). She did not have a record of previous cardiovascular disease. She was tachypnoeic (30 breaths/min) and febrile (38°C), with a pulse rate of 80 beats/min and blood pressure of 140/80 mm Hg. No peripheral oedema was present, but auscultation of her chest showed appreciable rhonchi in all areas and a few basal crepitations. A chest x ray film showed pulmonary oedema. Further investigations showed haemoglobin concentration 125 g/l, white cell count $12.1 \times 10^9/l$, and normal urea and electrolyte concentrations.

Case 3—This 99 year old woman did not have a record of previous cardiovascular disease. She responded only to painful stimuli and was severely dyspnoeic. She was sweaty, initially tachypnoeic (50 breaths/min),

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and cyanosed, with a tachycardia of 120 beats/min, a blood pressure of 130/100 mm Hg, and pinpoint pupils. No peripheral oedema was present, and the jugular venous pressure was not raised. Auscultation of the chest showed coarse crepitations, and she was coughing frothy sputum. Bowel sounds were noted to be active. An electrocardiogram showed atrial fibrillation (rate 120 beats/min) with left bundle branch block, and a chest x ray film confirmed pulmonary oedema. Further investigations showed a haemoglobin concentration of 130 g/l, white cell count $22 \times 10^9/l$, and normal urea and electrolyte concentrations.

POSSIBLE DIFFERENTIAL DIAGNOSES

Three differential diagnoses were considered. (1) Poisoning with an unknown agent resulting in a "cholinergic crisis," such as an organophosphorus insecticide. No such insecticides were kept on the ward. Symptoms of poisoning usually include diarrhoea and vomiting, which did not occur. (2) Poisoning with amanitas mushrooms: the symptoms usually include vomiting, and no mushrooms were present in the soup or main course. (3) Other causes of pulmonary oedema, such as acute ischaemic left ventricular failure, myocardial infarction, and inhalation of gastric contents, were unlikely given the history.

MANAGEMENT

One patient (case 1) simply required oral frusemide and a salbutamol nebuliser. The two others (cases 2 and 3) received intravenous frusemide (80 mg and 180 mg in two doses, respectively), oxygen, and intravenous aminophylline with little response. One (case 3) had also received diamorphine 2.5 mg intravenously, which had reduced the respiratory rate to 10/min and therefore required reversal with naloxone.

After discussion with the poisons unit at Guy's Hospital the patients in cases 2 and 3 were given 1-2 mg boluses of atropine intravenously every 15 minutes until they had dry flushed skin, dilated pupils, dry mouth, and tachycardia. The dose needed was 3.0 mg in case 2, 4.8 mg in case 3. Both patients improved within 30-40 minutes, and oral diuretics and salbutamol nebulisers were continued. The patients were further improved the next day: in particular, one (case 3) was cheerful and talking and did not have dyspnoea.

COURSE AND OUTCOME

Case 1—This patient continued to improve and was transferred back to West Park Hospital after two days.

Case 2—This patient's fever persisted, and despite physiotherapy and antibiotics she died on day 4. A coroner's postmortem examination showed: widespread bronchopneumonia, which histologically showed areas of early organisation and severe coronary atherosclerosis with 95% occlusion of the origin of the left anterior descending artery; histologically, the myocardium showed mild interstitial fibrosis. It was thought likely that the bronchopneumonia had pre-existed the ward episode, especially as she had been febrile on admission.

Case 3—After the initial improvement this patient developed a fever and productive cough on day 3. Despite physiotherapy and antibiotics her condition deteriorated and she died on day 8. A coroner's postmortem examination showed: bronchopneumonia in the posterior aspects of all lobes of both lungs and mild left ventricular hypertrophy with patchy interstitial fibrosis seen microscopically.

Investigations performed

TOXICOLOGICAL INVESTIGATIONS

Remains of meal

There was no soup left, and all soup containers had been washed before the investigation was started. Remains of the main course were analysed for pesticides, and none were detected. The absence of mushrooms was confirmed visually. The remains of the main course were not analysed for pilocarpine.

Oral aspirate from the worst affected patients

Oral aspirate was not analysed because of severe contamination with disinfectants. In addition, the aspirate could not be identified as having come from particular patients.

Blood and urine

Blood samples were taken for toxicological investigation from all three patients on arrival in the accident and emergency department before treatment and 12 hours later. Similarly, urine samples were taken on admission in cases 2 and 3 and 18 hours later in all three cases. These samples were sent to the Metropolitan Police Laboratory for possible identification of the responsible agent. Serum cholinesterase activities before and after the administration of atropine were measured in cases 2 and 3 and were within the normal range. These findings ruled out organophosphorus (anticholinesterase) poisoning.

Pilocarpine was identified in the urine specimens taken on admission from the two patients who later died. Pilocarpine eye drops packed in minims were stocked in the ward. Each minim holds roughly 14 drops, with each drop containing about 1.2 mg pilocarpine nitrate. Poisoning with this substance could produce the clinical features present in the affected patients. It was impossible to determine whether any minims were missing because investigations showed that more stocks were held than the records indicated. This had arisen because sometimes one minim dose was used for both eye drops, and neither was affected at the time of the incident.

In acute poisoning with pilocarpine the lethal dose in a healthy adult has been estimated to be as low as 60 mg,¹ but no deaths have been reported. Furthermore, methods for detecting and measuring pilocarpine in post-mortem specimens have not been reported. Two deaths after the injection of 10 mg pilocarpine were reported to have been due to hypersensitivity.²

There are no reports of the disposition, metabolism, and excretion of pilocarpine after oral consumption or of its detection in biological specimens such as blood and urine. Bayne *et al* reported a method for detecting pilocarpine in the aqueous humour of rabbits after topical application but did not mention its detection in other biological fluids.³ A modification of their method was used to identify pilocarpine in the urine specimens obtained on admission from the two patients who died. The method was based on gas chromatography after chemical derivatisation. Absolute identification was confirmed by gas chromatography—mass spectrometry. Analysis with this method of samples of water with pilocarpine added gave excellent detection limits, concentrations of 0.48 $\mu\text{mol/l}$ (0.1 $\mu\text{g/ml}$) and below being detected with ease. Somewhat surprisingly, though, the percentage recovery from urine specimens with pilocarpine added was low and estimated at less than 5%. Even with this relatively low sensitivity pilocarpine was detected in the urine specimens obtained on admission. It was not possible to detect low concentrations of pilocarpine in blood samples with this method.

POLICE INVESTIGATIONS

Police inquiries included interviewing ward staff and those with access to the room in which the drugs were kept. The mental state of most of the patients was such that they were unable to help. The police could not establish how the food came to be adulterated, although it was considered that human intervention had almost certainly been required.

Discussion

The main problem in the analysis of the postmortem findings in these cases was whether a causal relation existed between the events observed in the psychogeriatric ward and the subsequent deaths. In deciding the cause of death, which may form the basis of criminal proceedings, a pathologist must be mindful of the causal connection required by law between an alleged act and death. The requirement is that the act in question must have hastened death, albeit by a short time. Establishing this is not usually a problem, but as the time between the act and death increases, particularly when there is pre-existing disease so does the difficulty in establishing the requisite connection beyond all reasonable doubt.

The pattern of symptoms and signs and the fact that pilocarpine was detected in urine samples obtained from the two women who died left little doubt that they had suffered an episode of pilocarpine toxicity. In addition to causing bronchoconstriction pilocarpine causes bronchial mucus secretion.⁴ In case 2 these effects would have worsened the pre-existing bronchopneumonia and therefore accelerated death. In case 3 the effects of toxicity initiated a chain of events leading to bronchopneumonia and death.

At the combined inquests the Coroner recorded an open verdict in each case, accepting that the deaths were due to bronchopneumonia.

pneumonia after pilocarpine toxicity but declaring that there was no evidence as to where, when, or how the drug had been administered.

The Department of Health and Social Security has highlighted the ease of access to most hospitals⁵ and in 1982 asked health authorities to review their procedures for keeping equipment, stock, and premises secure and to develop a security strategy. There are no reports of hospital security in the United Kingdom, but the topic is occasionally aired in the United States. For example, Colling outlined incidents of rape, robbery, kidnapping, assault, and even homicide, which were occurring with increasing frequency on hospital campuses.⁶ He emphasised that a well organised security programme was essential for the provision of excellent patient care.

As food containers travel up to a third of a mile from the kitchen area to wards in West Park Hospital it was clear that tighter security was necessary. All the food containers are now sealed either with a plastic heat sealed bond or within a polythene bag sealed with a ratchet tag. The trolleys are also sealed around the body and doors. Food stores and ward larders are locked. Unauthorised access to any kitchen area, including those in the wards themselves, is prohibited; patients are not allowed in these areas. The capital cost of providing equipment to ensure the security of food was £43 000, with an annual cost of £3 500.

The practice of sometimes using one minim of eye drops to treat

both eyes was curtailed, thus improving the accuracy of ward pharmacy records.

As a coincidental safeguard food prepared in the hospital kitchen is sampled. These samples are frozen and retained for five days. This action was a consequence of the outbreak of food poisoning at the Stanley Royd Hospital near Wakefield.⁷

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References

- 1 Clarke EGC. Isolation and identification of drugs. *Pharmaceutical Press*. 1969;1:500-1.
- 2 André MJ. Two cases of fatal poisoning with pilocarpine in normal doses. *Confinia Neurologica* 1949;10:8-21.
- 3 Bayne WF, Chu LC, Tao FT. Subanogram assay for pilocarpine in biological fluids. *J Pharm Sci* 1976;65:1724-7.
- 4 Gilman AG, Goodman LS, Rall TW, Murad F. *Goodman and Gilman's the pharmacological basis of therapeutics*. 7th ed. New York: Macmillan, 1985:107.
- 5 Department of Health and Social Security. *Security*. London: DHSS, 1982. (HC(82)19.)
- 6 Colling RL. Security update, 1983. *Hospitals* 1983;57:76-9.
- 7 Department of Health and Social Security. Report of the committee of inquiry into an outbreak of food poisoning at Stanley Royd Hospital. London: HMSO, 1986.

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Lesson of the Week

Dangerous misuse of sulphonylureas

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Sulphonylureas are oral hypoglycaemic agents, widely prescribed for maturity onset diabetes in conjunction with dietary advice. The only serious metabolic side effect is frank hypoglycaemia, the frequency of which is often underestimated.^{1,2} Non-diabetics inadvertently ingesting oral hypoglycaemics will also be prone to such consequences, which may be profound and prolonged. The diagnosis will be less obvious and sometimes delayed in a patient with no history of having had hypoglycaemic tablets prescribed and no evidence of diabetes.

We present three such cases, in each of which there were difficulties in discovering that ingestion of sulphonylurea was the cause.

Case 1

A 65 year old woman was referred to the Hammersmith Hospital for further investigation of two episodes of hypoglycaemia, each of which had led to admission to the accident and emergency department of her local

Any patient admitted with unexplained severe hypoglycaemia of acute onset should have his or her medications checked—by scrutiny of the actual tablets—for inappropriate use of sulphonylurea

hospital because of unconsciousness the first time and restlessness and confusion the second. BM Stix (BM-Test Glycaemic) readings of capillary blood glucose concentrations were less than 1.1 mmol/l (19.8 mg/100 ml) (read by eye) on both occasions and she was resuscitated with intravenous dextrose, which had to be continued for a further 48 hours to prevent recurrent hypoglycaemia. There was no personal or family history of diabetes mellitus.

While being investigated at the Hammersmith Hospital for a possible islet cell tumour we found that she had unwittingly been taking 500 mg chlorpropamide a day. These tablets were contained in a box labelled "Acetazolamide," which had been prescribed for chronic glaucoma.

Assays of plasma from her second hypoglycaemic episode disclosed enormously and inappropriately raised insulin and C peptide concentrations—insulin 85.8 mU/l (normal fasting value <12 mU/l), C peptide 12.1 mg/l (grossly raised), and glucose 1.1 mmol/l (19.8 mg/100 ml).

Case 2

A previously fit 54 year old man was brought to the Hammersmith Hospital accident and emergency department unconscious. He was

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