PAPERS AND ORIGINALS

Value of emergency toxicological investigations in differential diagnosis of coma

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Summary and conclusions

Out of 208 cases of coma of unknown aetiology referred to the poisons unit of this hospital during 1978 for emergency toxicological investigations, 108 were found to be due to self-poisoning. Medical conditions, mainly neurological, accounted for coma in 90 patients; the cause was not ascertained in the remaining 10 cases. More than one preparation had been ingested by 58 (54%) of the poisoned patients, although barbiturates were the drugs most commonly encountered in the severe cases.

Toxicological investigations should be considered in the differential diagnosis of coma when history, physical examination, and emergency biochemical measurements yield little diagnostic information.

Introduction

Recent reports^{1 2} have drawn attention to the importance of toxicological investigations in differentially diagnosing coma. The aim of this study was to assess the value of such investigations in diagnosing coma in cases in which the help of the poisons unit was sought during 1978.

Patients and methods

We studied patients referred during 1978 in whom the sole indication of poisoning was the occurrence of coma. Thus we excluded all

cases in which self-poisoning was evident; patients with suspected cerebral anoxia secondary to drug intoxication, in whom toxicological investigations were performed as a prerequisite before stopping mechanical ventilation; and patients in whom coma was suspected as being a consequence of administering specific drugs in treatment. This last category included patients given drugs before parturition that were suspected of affecting the neonate. The hospital of origin of each request was noted.

Information obtained at the time of request included, when possible, the age and sex of the patient, whether mechanical ventilation was required, and the grade of coma. Coma was classified according to the response to painful stimuli,³ those patients in grade I coma (response to vocal commands) being excluded. Additional relevant details concerned drugs administered as treatment and the time that had elapsed between the presentation of coma and the despatch of samples for analysis. On receiving follow-up clinical information we re-evaluated each case with regard to any indications of poisoning at the time of the original request and also to the grade of coma.

TOXICOLOGICAL INVESTIGATIONS

Specimens of blood plasma or serum (5 ml), urine (20 ml), and gastric aspirate (when available) were requested in each case. Plasma or serum gas-liquid chromatographic (GLC) assays were used for the following groups of drugs: barbiturate hypnotics, glutethimide, methaqualone, and meprobamate⁴; phenobarbitone, primidone, and phenytoin⁵; ethchlorvynol, chlormethiazole, and trichloroethanol⁶; benzodiazepines⁷; and ethanol and methanol.⁸ Paracetamol and salicylate were tested for by urine spot tests⁹; amphetamines, monoamine oxidase inhibitors, etc, by a urine or gastric aspirate GLC assay (R J Flanagan and D M Rutherford, unpublished work); and tricyclic antidepressants, antihistamines, narcotics, phenothiazines, parasympatholytics, and some other compounds by a similar procedure (R J Flanagan, D A Mansell, and D M Rutherford, unpublished work) together with spot tests and thin-layer chromatographic analysis⁹ when necessary. Additional tests were performed if possible when specifically indicated.

Plasma or serum paracetamol¹⁰ and salicylate¹¹ concentrations were measured when relevant, and the concentrations of the drugs and drug metabolites detected using the plasma or serum GLC assays were also measured. In those patients in whom plasma drug concentrations could not be measured coma was considered to be due to poisoning when drugs other than those given as treatment were detected in the samples analysed and no other cause for coma was found. In each case

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the diagnosis of poisoning as the cause of unconsciousness was verified by follow-up information received.

Requests for analyses were scrutinised by experienced laboratory or medical staff in an attempt to ensure the clinical relevance of all investigations. Once authorised, the analyses were performed immediately, the results normally being made available within one to three hours of receipt of the specimens. Analyses performed outside normal laboratory hours were noted.

Results

Follow-up information was insufficient in 19 cases in which analyses were performed. Of the remaining 208 patients, most (193) were admitted in coma, although 15 became unconscious while in hospital. At the time the samples were obtained 110 (53%) of all the patients were in grade IV coma, and 61 (55%) of these required mechanical ventilation. Of the remaining patients, 62 (30%) and 36 (17%) were in grade III and grade II coma respectively. The time between admission or onset of coma and the despatch of specimens for analysis varied from 72 hours to less than one hour, although was mostly under 24 hours. Forty-six (22%) of the analyses were undertaken outside normal laboratory hours. Cases were referred from 66 hospitals, of which 24 were outside the Greater London area. Twenty-nine (14%) of the analyses were undertaken for these 24 hospitals.

CAUSES OF COMA

Acute poisoning was found to be responsible for the coma in 108 patients (52% of those studied), although in two cases (in which lithium and trichloroethanol, respectively, had been ingested) the diagnosis was made after our investigations. Two patients poisoned themselves while in hospital; in one the overdose (of amitriptyline) was severe enough to cause a cardiac arrest.

Fifty-eight poisoned patients had ingested more than one agent (table I). Barbiturates were the single agent detected most often

TABLE I—Frequency of multiple drug ingestion

No of agents ingested:	1	2	3	4	5
No of patients:	50	36	14	5	3

(table II), with amylobarbitone and quinalbarbitone constituting 51% of the barbiturates ingested. Paracetamol, and paracetamol and dextropropoxyphene preparations, constituted 58% of the analgesic drugs ingested, while salicylate constituted 21%. Of the benzodiazepines, diazepam was most commonly found (in 65% of cases), followed by nitrazepam (19%) and flurazepam (15%).

Mechanical ventilation was required for 25 patients, in 15 of whom barbiturates were the principal agents ingested. In all, 13 patients suffered cardiorespiratory arrests, which proved fatal in seven cases, and three further drug-induced deaths occurred. Barbiturates and paracetamol and dextropropoxyphene preparations were the drugs most commonly found in these fatal cases.

TABLE II—Drugs or drug groups detected in poisoned patients. (Numbers in parentheses indicate numbers of cases in which only one agent was ingested)

	No of patients in whom drug detected
Barbiturates	51 (20)
Non-barbiturate hypnotics (eg, glutethimide)	7 (3)
Benzodiazepines	54 (5)
Ethanol	21 (10)
Anticonvulsants, excluding phenobarbitone	3
Tricyclic antidepressants	18 (4)
Phenothiazines	12 (1)
Analgesics	19 (4)
Antihistamines	4
Others*	9 (3)

* Chlorprothixene (1), diethylpropion (1), digoxin (1), lithium (1), orphenadrine (2), phenylbutazone (1), and quinine (2).

As a direct result of toxicological investigations three patients underwent forced alkaline diuresis, one was haemoperfused, and at least four were given specific antidotes. On the other hand, five poisoned patients underwent lumbar puncture and a further three underwent computerised axial tomography before toxicological analyses were requested.

Table III shows the eventual diagnoses in the 100 remaining patients, who were not poisoned. Neurological conditions accounted

TABLE III—Details of six classifications made in non-poisoned patients, and diagnoses. Figures in parentheses indicate numbers of deaths

	No of patients
Neurological	
Cerebrovascular:	
Cerebral haemorrhage or thrombosis	16 (12)
Subarachnoid haemorrhage	8 (4)
Subdural haematoma	4 (3)
Infections:	
Encephalitis	8
Meningitis:	
Viral	1
Tuberculous	1
Brain abscess	1
Others:	
Head injury	4 (1)
"Encephalopathy" (3 Reye's syndrome)	7 (3)
Postictal coma	4
Cerebral metastases	1 (1)
Psychiatric	
Hysteria	4
Fugue state	1
Cardiorespiratory	
Pneumonia or bronchopneumonia	8 (5)
After cardiorespiratory arrest (not drug-induced)	5 (5)
Complete heart block	1
Heart failure	1 (1)
Metabolic or endocrine	
Hypoglycaemia	5 (1)
Diabetic ketoacidosis	2
Renal failure (uraemia)	2 (2)
Hepatic failure	1 (1)
Miscellaneous	
Hypothermia	1
Septicaemia	1 (1)
Asphyxia	1 (1)
Cot death	1
Postanaesthetic	1
Unknown	10 (1)

for coma in 55. Forty-three of the non-poisoned patients died, including one of the 10 in whom the cause of coma was not ascertained. This patient required mechanical ventilation, as did 35 of the others. Four non-poisoned patients received gastric lavage. The persistence of coma despite early diagnosis and treatment led to toxicological investigations in eight patients with metabolic disorders. In the remaining two patients in this group the eventual diagnoses (hypoglycaemia and hepatic failure, respectively) were made after our investigations.

AGE AND SEX DISTRIBUTIONS

We did not know the ages of 11 poisoned and seven non-poisoned patients. Table IV shows the age and sex distributions of the remaining patients. The ages of the poisoned patients ranged from 2 to 86 years, and the non-poisoned group showed a similar distribution

TABLE IV—Age and sex distributions in 190 of the patients for whom investigations carried out*

Age group (years):	0-4	5-9	10-19	20-29	30-39	40-49	50-59	60-
Poisoned patients								
Male	1	4	6	18	10	10	3	2
Female	3	7	12	3	3	5	10	
Non-poisoned patients								
Male	6	4	7	7	3	5	3	2
Female	5	4	7	9	6	9	8	8

* Ages of 11 poisoned and seven non-poisoned patients unknown.

(range 3 months to 82 years). In the age range 20-49 years 56 (59%) patients were comatose as a result of poisoning, whereas in patients aged under 10 coma was more commonly caused by medical conditions (70%).

Discussion

Little information exists on the incidence of poisoning as a cause of coma presenting without obvious explanation, although it was found to be 25% in one series.¹² Despite the increasing incidence of self-poisoning, which now accounts for over 10% of acute medical admissions,¹³ it is perhaps surprising that drug intoxication was responsible for coma in over half of the patients studied here. Although coma occurring in patients already in hospital was often due to medical causes, two patients poisoned themselves while in hospital, in one case causing a cardiac arrest.

The incidence of multiple drug ingestion in the poisoned patients (table II) was in keeping with other reports.¹⁴⁻¹⁵ Barbiturate overdose was responsible for 60% of the severe cases of poisoning (patients in grade IV coma requiring mechanical ventilation) and contributed to four deaths. These findings are consistent with others relating to coma in acute poisoning.¹⁶ Moreover, the importance of suspecting barbiturate intoxication in coma of unknown aetiology has been emphasised¹⁷ and would appear to be still relevant despite reports advocating caution in prescribing these drugs.¹⁸⁻¹⁹

The dangers of overdosage with preparations containing dextropropoxyphene have been emphasised,²⁰⁻²¹ and such preparations had been ingested either alone or with other agents in three of the fatal cases described here. Naloxone rapidly reverses the cardiac and respiratory depressant effects of narcotics such as dextropropoxyphene²²⁻²³ and should be used as both a diagnostic and a therapeutic agent when narcotic-induced coma is suspected. All three patients, however, suffered cardiorespiratory arrests either immediately before or on admission to hospital, and in these cases, when coma was subsequently attributed to anoxic cerebral damage, laboratory identification of the drugs ingested remained the only way of diagnosing narcotic poisoning.

Although most of the cases originated from hospitals within Greater London owing to both the proximity of these hospitals to this unit and the population density of the area, the incidence of poisoning and the types of drug encountered were similar in cases referred from other hospitals. Ethanol or barbiturate poisonings, or both, were responsible either solely or in part for 72 (67%) cases of drug-induced coma (table II). Laboratory facilities for detecting and measuring these compounds are generally available in most district general hospitals,²⁴ and laboratory investigations might be expected to yield useful diagnostic information in a high proportion of patients with coma of uncertain cause. Few hospital laboratories, however, have the required equipment and skill to discern or exclude poisoning by drugs such as the non-barbiturate hypnotics, benzodiazepines, and tricyclic antidepressants. This emphasises the need for a central laboratory service capable of undertaking such analyses on an emergency basis.

In one case, in which trichloroethanol had been ingested, information on self-poisoning was obtained from the patient on recovery rather than from our analyses. The only other case of poisoning not detected by our analyses was one in which the patient died after ingesting lithium carbonate; this is a drug that we cannot easily incorporate into our scheme of analysis. We now discuss the possibility of lithium poisoning with the requesting clinicians and ensure that serum or urinary lithium concentrations are measured when indicated.

The potential for error in emergency toxicological analyses is large, especially when several cases are being analysed simultaneously, and the consequences of gross error, if not always life threatening, can nevertheless be serious.¹⁻² Thus we find it essential not only to discuss the interpretation of our findings with the appropriate doctor on completing an analysis but also

to attempt to follow up each case actively. If clinical opinion still suggests a possibility of poisoning despite negative toxicological results further analyses are undertaken should the diagnosis remain a cause for concern. Accurate clinical information is essential to avoid unnecessary analyses in patients with metabolic disorders, such as the case in which hypoglycaemia was diagnosed and successfully treated only after exclusion of poisoning.

Newton argued²⁵ that unconsciousness in a patient aged 15-55 years who has had no head injury is almost certainly due to drug overdosage. In the present study, however, only 56% of the patients within the age range 20-59 were comatose as a result of drug intoxication, and, in fact, the age distributions shown by both the poisoned and non-poisoned patients were similar over the entire age range (table IV).

We emphasise that these investigations were undertaken for diagnostic purposes, and, since good supportive care is the basis of management in patients poisoned with centrally depressant drugs, it is not surprising that only eight poisoned patients received specific treatment as a result of toxicological analyses. When faced with an unconscious patient, however, early diagnosis is important in order to ascertain whether the underlying condition is directly treatable or whether further clinical investigations are required. Earlier toxicological investigations in the poisoned patients who underwent lumbar punctures and computerised axial tomography would have obviated the need for these tests. Thus the results of this study suggest that in cases of coma in which history, physical examination, and emergency biochemical investigations yield little diagnostic information toxicological investigations should be instituted promptly.

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