conventional treatment. The place of alcohol in treating paracetamol overdose requires further investigation.

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THEOPHYLLINE POISONING

SIR,—Clinicians may see theophylline self-poisoning more often in future, as a result of the increased therapeutic use of this drug particularly in its sustained release form. The clinical features of theophylline overdose include nausea and vomiting, abdominal pain, haematemesis, hypotension, tachyarrhythmias, and CNS stimulation, including convulsions. The case fatality rate has been reported to be high, particularly in those who have had a convulsion,[1] though this is difficult to determine accurately because few unselected series of patients have been reported. We wish to focus attention on three important aspects of theophylline poisoning and its management, based on experience of a large number of cases and illustrated by the last twelve consecutive admissions to the West Midlands poisons unit (table).

Firstly, in those who have ingested a sustained release preparation a single early plasma theophylline measurement will not reflect accurately the degree of intoxication, and the doctor may not appreciate the potential seriousness of the overdose. For example, the plasma theophylline level in case 8 rose from 46 to 161 mg/l by 8 h after the patient's admission.

Secondly, a marked transient hypokalaemia is a frequent complication of theophylline poisoning. Although hypokalaemia has been observed previously it has not attracted special interest. This is surprising since it may be a major factor in the genesis of dysrhythmias and possibly of convulsions. Our observations indicate that urinary excretion of potassium is not increased in theophylline poisoning. Theophylline probably causes redistribution of potassium into cells at the expense of the extracellular pool, an effect reinforced by the increased catecholamine response, and mediated by an increased intracellular 3,5-cAMP concentration, hyperinsulinism, and hyperglycaemia.[2,3] The analagous hypokalaemia seen in dose[4,5] and overdose[6,7] with β_2-adrenoceptor agonists has been explained in a similar manner.

Thirdly, intensive supportive measures including frequent monitoring of electrolyte status and correction of hypokalaemia may obviate the need for haemoperfusion. Weinberger and Hendeles[8] have recommended that haemoperfusion should be used if the plasma theophylline concentration is greater than 60 mg/l. More recently, Park et al[9] have suggested that patients with theophylline plasma concentrations between 30 and 60 mg/l should undergo haemoperfusion if, in addition, they are over 60 years, have significant liver disease and/or congestive heart failure, and a theophylline half-life of 24 h or more.

Although we have had considerable experience of haemoperfusion in the management of poisoned patients, we used it only twice in this series and in both cases without regard to the plasma theophylline concentration. Patients 1 and 5 were haemoperfused for intractable severe vomiting. Patient 1 had ventricular bigeminy and trigeminy and had a convulsion while hypokalaemic, though the peak plasma theophylline concentration was only 66 mg/l. All twelve patients in the series survived without complications. Our observations suggest that a successful outcome will occur without serious sequelae in most patients with the use of supportive measures alone. This is important since haemoperfusion is not widely available on an emergency basis. We suggest that, as in most other circumstances, clinical considerations rather than plasma concentrations alone should determine whether or not haemoperfusion should be used. Correction of hypokalaemia may stabilise the patient cardiologically and neurologically and obviate the need for haemoperfusion. However, in a patient distressed by severe vomiting, resistant to antiemetics, haemoperfusion should be considered.

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TOXICITY OF SALBUTAMOL AND THEOPHYLLINE TOGETHER

SIR,—Slow-release preparations of theophylline are now frequently used in self-poisoning,[1] and concern has been expressed that the combination of theophylline with beta-adrenergic bronchodilators may cause fatal cardiac arrhythmias.[2-4] However,

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CLINICAL FEATURES, SERUM POTASSIUM LEVELS, AND PHARMACOKINETIC DATA IN TWELVE CASES OF THEOPHYLLINE OVERDOSE

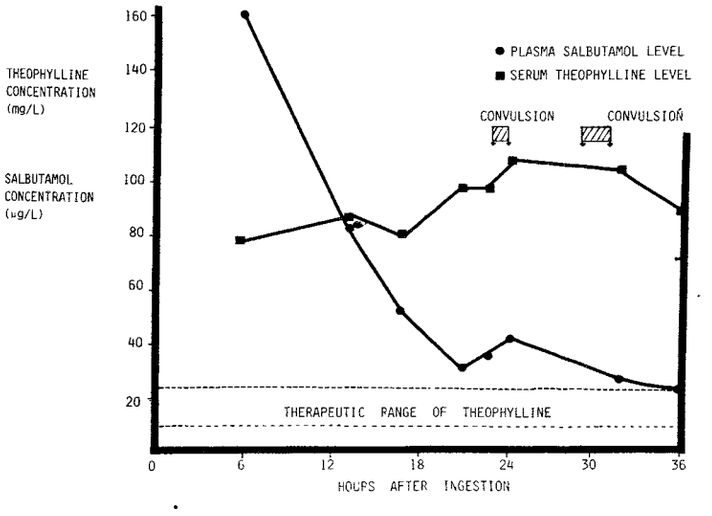
—	Case											
	1	2	3	4	5	6	7	8	9	10	11	12
Sex	F	F	F	F	F	F	M	F	M	F	F	M
Age (yr)	15	16	16	19	20	24	25	26	30	38	60	74
Nausea and vomiting	+	+	+	+	+	+	+	+	+	+	+	+
Sinus tachycardia	+	+	+	+	+	+	+	+	+	+	+	+
Supraventricular tachycardia	+										+	
Ventricular bigeminy and trigeminy	+											
Abdominal pain	+		+			+				+		
GI haemorrhage								+		+		
Restlessness and agitation	+		+	+	+					+		+
Tremor	+					+		+		+	+	
Convulsions	+									+		+
Admission serum potassium (mmol/l)	2·5	3·1	2·4	2·9	2·7	3·0	3·3	2·8	—	3·0	—	2·6
Peak theophylline conc (mg/l)	66	65	71	68	75	80	64	161	70	99	73	78
Time of peak from ingestion (h)	9	7	2	4·5	9*	8	10†	12	5	18*	15*	7
Terminal elimination half-life (h)	6‡	10	6·5	9	—	5	13	11	†	15	11	12

*Maximum concentration recorded on admission †Patient discharged himself when plasma concentration was 59 mg/l. ‡Post-perfusion.

we have seen a case in which massive overdoses of sustained-release aminophylline and salbutamol together had no important cardiac effects.

A healthy 26-year-old man admitted with stupor, vomiting, and haematemesis following a drinking bout showed tremulousness, restlessness, and persisting bilious vomiting with a sinus tachycardia (180 beats/min), and blood pressure 110/70 mm Hg. Routine poisons screen was negative. His serum potassium was initially 2·2 mmol/l, but this was easily corrected, and serum biochemical values remained normal thereafter. 3 h later he said he had taken unspecified amounts of salbutamol (Ventolin') and aminophylline ('Phyllocontin') tablets approximately 9 h earlier. Despite repeated boluses of metoprolol, intravenously to a total of 35 mg, the tremor and tachycardia were unaffected. 24 h after ingestion he had an unheralded episode of severe status epilepticus. 150 mg intramuscular phenytoin and 45 mg diazepam were without effect. The seizures abated after 560 mg intravenous chlormethiazole ('Heminevrin'), but respiratory depression then necessitated artificial ventilation. 6 h later another status epilepticus was uninfluenced by neuromuscular blockade with 4 mg pancuronium. 1600 mg chlormethiazole then precipitated acute circulatory collapse. Widespread muscular tears could now be palpated, and the serum potassium rose uncontrollably to 8·0 mmol/l, when his heart stopped in systole. At necropsy a 7 cm×8 cm bezoar of tablets was present in the stomach. There was gross macroscopic and microscopic muscle damage.

The figure shows the course of the plasma levels of salbutamol and theophylline found on later analysis. These show that both



Plasma salbutamol and serum theophylline levels during treatment.

drugs were at extremely toxic levels on admission and that the salbutamol concentration fell in an exponential fashion with a normal half-life of 6·5 h. In sharp contrast, theophylline concentrations rose steadily until he convulsed. The remarkably long period of absorption is probably due more to the size of the initial dose and its retention in the stomach than to the characteristics of the sustained-release preparation.[4]

Although the patient was monitored in an intensive-care unit, the lethal effects of theophylline were quite unheralded, emphasising that clinical assessment alone is not a sufficient guide and that theophylline concentrations must be measured. By contrast, the severe salbutamol poisoning, even in the presence of toxic levels of theophylline, proved much less harmful. Nevertheless, it must be noted that this patient was neither hypoxic nor acidotic at these very high levels, and this might prove a critically important difference in young asthmatics.

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FUNCTIONAL T_4 HELPER CELLS IN PATIENT WITH HTLV RELATED SÉZARY SYNDROME

SIR,—Most T cell lymphosarcoma-leukaemias, especially those in Japan, and rare cases of Sézary syndrome are related to infection with a human retrovirus (HTLV) with tropism for cells belonging to the inducer-helper T subset (T_4).[1] However, functional studies show that these leukaemic cells mediate a suppressive effect on B cell differentiation,[2] while HTLV may be involved in the pathogenesis of acquired immunodeficiency syndrome, in which a striking decrease of circulating T_4 cells is a feature.[3,4] These findings suggest either that HTLV infects a subset of T_4 cells with suppressive (or suppressive-inducer) functions or that infection impairs T_4 helper function and eventually destroys these cells. We describe here a case of HTLV-related Sézary syndrome where the abnormal cells retain their helper function—ie, they were able to help B cells to differentiate to Ig-secreting cells.

A 55-year-old Black woman, born in and living on Martinique, presented with a 1 year history of skin nodules and slight cervical, axillary and inguinal lymphadenopathy. WBC was 7500/µl with 50% lymphoid cells. Typical Sézary cells (large and small variants) were observed on the blood film and node aspirate. Biopsy of a skin lesion was entirely compatible with cutaneous lymphoma: there was a dense lymphoid infiltrate with epidermotropism and Pautrier microabscesses. The patient was treated with steroids and chlorambucil with a marked improvement.

90% of this patient's blood lymphocytes expressed the T_4 antigen, whereas a subset of them were Ia positive (30%) or had a receptor for interleukin 2 (57%) as shown by their reactivity with the TAC monoclonal antibody.[5] This phenotype is unusual for Sézary cells and more like that of Japanese ATL.[6] Careful review of the haematological and clinical data, however, supported the diagnosis of Sézary syndrome. Whether or not this phenotype may be indicative of a subset of T cell malignancies related to HTLV infection remains to be determined.

These Sézary cells produced HTLV in culture, as shown by the expression at their surface of p19 and p24 proteins (demonstrated by indirect immunofluorescence with specific antibodies kindly provided by Dr R. C. Gallo) as well as by the detection in the supernatant of magnesium dependent $HTLV_1$ related reverse transcriptase. Antibodies to HTLV p24 were present in the serum at a titre of 5000 by a radioimmunoassay using purified p24 (Dr L. Schaffar-Deshayes). This is the third case of Sézary syndrome with HTLV infection. In a recent study only 2 of 251 sera from Sézary patients had HTLV antibodies.[1] That our patient was native from

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CO-CULTURE EXPERIMENTS BETWEEN NORMAL B CELLS AND AUTOLOGOUS T CELLS OR SÉZARY CELLS

Cells cultured with 5×10^5 B cells and pokeweed mitogen	% cells with cytoplasmic Ig* at day 7 of culture
None	4
Autologous T cells 5×10^5	27
Autologous T cells 1×10^5	25
Sézary cells 1×10^6	17
Sézary cells 5×10^5	20
Sézary cells 1×10^5	24

*As assessed by direct immunofluorescence on fixed cells with a polyvalent anti-human-Ig serum.