Multi-centre studies are in progress to clarify a possible association between Reye's syndrome and aspirin use by feverish children. In June 1986, the Committee on Safety of Medicines, in a letter to all doctors, announced that it had 'considered the available evidence and concluded that, while the causes of Reye's syndrome are not clearly defined, aspirin may be a contributory factor to the causation of Reye's syndrome in some children'. It considered it 'prudent to avoid giving aspirin to children under twelve years old unless specifically indicated'. Reye's syndrome is a rare acute encephalopathy associated with fatty change of the liver and occurring typically after viral infections. The clinical features may include vomiting and any degree of impaired consciousness.¹

The following case history demonstrates that aspirin, when administered to children for straightforward febrile illness, even in the recommended dosage, can cause serious illness due to raised blood salicylate levels, quite apart from Reye's syndrome.

CASE HISTORY

A three-year-old boy was admitted to another hospital in April 1984 in a semi-conscious state. For four days he had been lethargic with a dry cough and decreased appetite. Three days prior to admission he had developed vomiting and pyrexia, for which his family doctor had prescribed 300 mg of acetylsalicylic acid three times daily. Twenty-four hours prior to admission the boy became drowsy with grunting respirations, and at 2.00am on the morning of admission his parents found him in a stiffened position, with eyes rolling and teeth clenched, unresponsive to their voices.

On admission he was clinically dehydrated with rapid, grunting respirations. His breath smelt ketotic. He was unresponsive to non-painful stimuli. His pupils were of normal size and reacted sluggishly to light. There was generalised hypotonia. Blood sampling revealed a relative lymphocytosis, metabolic acidosis, normal blood sugar, normal liver function tests, increased prothrombin time and normal serum ammonia. Blood salicylate level was 537 mg/l (forced alkaline diuresis is normally indicated at levels of greater than 350 mg/l). Chest X-ray was clear and cultures of blood, cerebrospinal fluid and urine were to prove sterile.
The boy's stomach was washed out, intramuscular vitamin K$_1$ was administered and intravenous 4.5% sodium bicarbonate and diuretics were commenced. Seventeen hours following admission the urinary pH had risen to 7.0. The intravenous infusion was changed to 0.18% sodium chloride, 4% dextrose and potassium supplements. Twenty-four hours following admission his condition had deteriorated. His pupils were dilated but still reacting to light, blood pressure was raised and there was early papilloedema. 30ml of 20% mannitol were administered intravenously and fluid input was restricted. Crepitations were audible at both lung bases and chest X-ray showed early pulmonary oedema. Additional intravenous frusemide was administered and transfer to the Royal Belfast Hospital for Sick Children was arranged. Before transport arrived, the boy's temperature rose to 39°C and he suffered a three-minute generalised seizure, treated successfully with intravenous diazepam. On arrival at the Royal Belfast Hospital for Sick Children intensive care unit a further convulsion required intravenous diazepam and phenytoin, and endotracheal intubation followed by intermittent positive pressure ventilation for subsequent cyanosis and decreased consciousness. Ventilatory requirements were low and extubation was possible 48 hours later. He was later transferred back to the referring hospital where diuretics were stopped on the thirteenth day after first admission. Phenytoin was discontinued two months after discharge. There have been no further fits and both physical and developmental follow-up since have been normal.

**DISCUSSION**

In 1974, of a total of six cases of aspirin overdose admitted to the Royal Belfast Hospital for Sick Children, three were accidental and three therapeutic. This picture changed rapidly as a result of the introduction of child-resistant containers in 1976,$^{2,3}$ smaller pack sizes and attempts to eliminate attractively-coloured tablets. A review of admissions in a one-year period a decade later revealed five cases of aspirin poisoning, all of whom had had the drug either prescribed by a medical practitioner or given to them by their parents without medical advice. With only one exception aspirin had been administered in the recommended dosage for age. Despite this the five patients' blood salicylate levels ranged from 300 to 600mg/l and all required (at least) forced alkaline diuresis. Aspirin is poorly soluble in the acid solution in the stomach and may precipitate out, forming a coating on the stomach wall from which slow absorption can take place. This underlines the importance of stomach washouts as soon as possible after ingestion of large amounts of aspirin.

Salicylates directly stimulate the respiratory centre causing a respiratory alkalosis and a compensatory metabolic acidosis. They alter the function of the Krebs cycle to bring about an accumulation of lactate and decouple oxidative phosphorylation so that energy is wasted as hyperpyrexia. Bleeding may result from local gastrointestinal irritation, altered platelet function or defective prothrombin synthesis. Hypokalaemia may be due to a direct effect on the renal tubular mechanism, or indirectly from the respiratory alkalosis. Hypoglycaemia or hyperglycaemia may occur, the former is the more serious clinically. In general, the three cardinal symptoms are vomiting, hyperventilation and hyperthermia, and aspirin poisoning should always be considered when these coincide in a child.$^{4,5}$

There has been much debate about a possible association between Reye's syndrome and aspirin.$^6$ The connection does not appear to be dose-related$^7$ but the ages of children who suffer from Reye's syndrome during influenza epidemics

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Aspirin overdose

have been found to correlate more closely with the age distribution of aspirin use than with that of influenza.8,9,10 Involvement of the central nervous system11 and liver12,13 occurs both in aspirin overdose and Reye's syndrome and parallels have been drawn between the various toxic metabolites which accumulate in both conditions.14,15

If there is a causal relationship between aspirin and Reye's syndrome, there should be a decline in cases as aspirin use is restricted. However, epidemic rates of the viral illnesses which precede Reye's syndrome may change, and the rate of reporting of Reye's syndrome by physicians may increase as more doctors become aware of it.16 In any case, Reye's syndrome or not, the preceding history demonstrates that the decision to limit the use of aspirin for simple febrile childhood illnesses has been a wise one.

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