Discussion

This study shows that a false increase in serum catecholamine induced by the administration of methyldopa level can be reduced by the simultaneous administration of barbiturate. Presumably methyldopa metabolism is accelerated by barbiturate. Buhs *et al.* (1964) showed that in man about half of ingested methyldopa is absorbed and that 50-90% of the amount absorbed is excreted within 48 hours. Of the metabolities methyldopa-mono-O-sulphate is found in largest quantities, and most probably the site of this phase of breakdown is the liver. Smaller amounts of 3-O-methyl-alphamethyldopa are demonstrable in the urine, and also alphamethyldopamine in the so-called neutral fraction, which is actually the first stage of methyldopa metabolism in man.

Since at least part of methyldopa metabolism takes place in the liver and the effect of barbiturates on the microsomal enzymes of the liver has been proved, we suggest that methyldopa metabolism may be accelerated by barbiturates through enzyme induction. This phenomenon may have practical implications in the treatment of hypertensive patients.

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MEDICAL MEMORANDA

Strychnine Poisoning Treated Successfully with Diazepam

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We report the use of diazepam in the emergency management of strychnine poisoning.

Case History

A West Indian child aged 13 months was found playing with white tablets and had one in his mouth. Fifteen minutes later he screamed loudly and became rigid. He remained rigid with intermittent crying until in the ambulance on the way to hospital, when he had a convulsion and a respiratory arrest. He was given mouth-to-mouth resuscitation and external cardiac massage. In the casualty department he continued to have fits repetitively and had five brief respiratory arrests within a short space of time. His airway was maintained and oxygen was given. During these convulsions he remained conscious and had facial grimacing with opisthotonos. At this time the nature of the tablets was unknown.

Diazepam 2·5 mg given subcutaneously did not produce relaxation, but 2·5 mg intravenously, given in the course of an episode of severe muscle spasm complicated by respiratory arrest, produced immediate relaxation. His reflexes were still exaggerated and occasional extensor thrusts were evoked by minimal stimuli. By this time the tablets were morphologically identified as Easton's syrup (later confirmed by chromatography). Endotracheal intubation was carried out after the intravenous administration of suxamethonium and he was maintained with 100% oxygen and intermittent positive-pressure respiration. Gastric lavage was performed with sodium bicarbonate solution 45 minutes after ingestion of Easton's syrup tablets. An intramuscular injection of desferrioxamine mesylate was given because of the iron content of the tablets.

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The child continued to be hyperreflexic but was breathing spontaneously, and intermittent positive-pressure respiration was discontinued. No more convulsions occurred, and six hours later the endotracheal tube was removed. He had a residual croup which was treated with ampicillin and he was discharged after seven days. Follow-up two months later showed no obvious neurological sequelae.

Comment

Easton's syrup tablets have long been regarded as "tonics." They are available in two strengths (*Martindale's Extra Pharmacopoeia*, 1967). Formula A contains iron phosphate 200 mg, quinine sulphate 50 mg, and strychnine hydrochloride 1 mg, while formula B is half this strength. Formula A is the widely used tablet and is dispensed in a sugar-coated form which is particularly attractive to children (Southby, 1965).

Strychnine produces excitation of all portions of the central nervous system by increasing the level of neuronal excitability as a direct result of selectively blocking inhibition (Goodman and Gilman, 1970). Nerve impulses are therefore enhanced. The convulsions occurring as a result of this decreased inhibition are characterized by tonic extension of the body and all limbs in a symmetrical fashion. These intermittent thrusts are initiated by any sensory stimulus, usually when the strychnine concentration is lower than that required for a sustained tonic convulsion. Further toxic effects involve contractions of the diaphragmatic, thoracic, and abdominal muscles, leading to respiratory arrest. The ensuing hypoxaemia finally results in the terminal medullary paralysis (Thienes and Haley, 1964).

Tolerance to strychnine is variable. As little as 2 mg has proved to be unpleasant and 15 mg has caused death. Nevertheless, recovery has been reported with an intake of 1 g and over (Thienes and Haley, 1964). Based on the mother's memory, we believe the intake in this case to be between 10 and 20 tablets, equivalent to between 10 and 20 mg of strychnine.

The standard management has long rested on the prevention of convulsions and support of respiration by relying on depressants of the central nervous system which sufficiently antagonize strychnine to allow respiration to continue (Thienes and Haley, 1964; Goodman and Gilman, 1970). The use of intravenous barbiturates and endotracheal intubation with intermittent positive-pressure respiration has been found to be effective (Statham, 1956; Hawkins, 1962).

The role of diazepam as an anticonvulsant has been reviewed by Brett (1970). We could find only one previous record of its use in strychnine poisoning (Heidrich and Ibe, 1969). Diazepam has an inhibitory effect on polysynaptic reflexes in the spinal

cord believed to be by elective increase of presynaptic inhibition mechanisms. It therefore acts specifically against the decrease of the inhibitory mechanisms released by strychnine and blocks the transfer of the increased impulses between spinal segments. Diazepam thus limits the need for prolonged general anaesthesia with controlled breathing to the really severe cases.

Pharmacological textbooks (Laurence, 1966; Goodman and Gilman, 1970) seem universal in their condemnation of strychnine as a therapeutic drug. There is no justification for the presence of any strychnine-containing compound in therapeutic usage, and we urgently suggest that immediate withdrawal be enforced.

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Case of Poisoning from Red Whelk

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Paralytic shellfish poisoning is rare in the United Kingdom, the most recent outbreak being that in 1968 in north-east England (McCollum *et al.*, 1968), when 78 cases were reported, the cause being common mussels which had concentrated the toxin produced by *Gonyaulax tamarensis*, a dinoflagellate. A case of poisoning by *Neptunea antiqua* was suspected in 1969 (Wood, 1970), but the issue was confused at that time owing to the prevalence of toxin in mussels consequent on an efflorescence of *G. tamarensis*.

A unique case of poisoning by tetramine, a toxin produced in the salivary glands of *N. antiqua*, the red whelk, occurred in Fife in the summer of 1970.

Case History

A young adult man was admitted to hospital at 7 p.m. suffering from a curare-like poisoning. At lunch time he had eaten red whelks which had been boiled and removed from the shells. One hour later blurred vision and diplopia had developed, followed by tingling of the hands and feet and twitching of the calf muscles. Coarse muscular twitching and weakness of the limbs developed into paralysis and collapse. Three and a half hours after the meal he had a violent attack of vomiting lasting about half an hour, followed by acute proctalgia lasting about five minutes but without defecation or diarrhoea. Further vomiting occurred in the ambulance bringing him to hospital. The patient also complained of vague lower abdominal pain. After his admission the symptoms became less severe and improvement was rapid, the patient being fully recovered and mobile in 24 hours. Examination of the abdomen and nervous system showed nothing abnormal. He was discharged after 48 hours' observation, no further symptoms having developed.

A shell was identified at the Gatty Marine Laboratory, St. Andrews, as one of the whelk family, *N. antiqua*, which secretes the toxin tetramine in its salivary glands (Halstead, 1965). Several other members of the whelk family also secrete tetramine.

Comment

N. antiqua is a non-littoral species, ranging from the shallows to depths of up to 100 fathoms (183 m), and is not normally seen by persons collecting shellfish on the shore. Its size, however, might make it attractive if found, as a shell can yield up to about 80 g of edible meat.

There is very little information available on tetramine poisoning in man after the consumption of whelks related to *N. antiqua*. The only toxicity data available are for mice, which indicate a seasonal variation ranging from 240 mouse units in September to a maximum of 430 mouse units in July. The toxin appears to be confined to the salivary ducts of the organism, and it is possible that removal of the ducts before consumption would eliminate the risk of poisoning (Fänge, 1960).

Jeffreys (1867) stated that in the second half of the nineteenth century whelks, including the red whelk or almond (*N. antiqua*), were regarded as a delicacy by the lower working classes in London but did not mention any known noxious effects at that time. Boulenger and Boulenger estimated the value of whelk fisheries in England at £25,000 per annum in 1914. The whelks were used principally as bait and occupied only a very secondary position as food. Related species, *N. arthritica* and *N. intersculpta*, have been reported as producing numerous intoxications in Japan (Asano and Ito, 1960).

Intoxication results when the glands of whole shellfish are ingested either raw or cooked or from cans. The clinical characteristics of whelk poisoning may be nausea, vomiting, anorexia, weakness, fatigue, faintness, dizziness, photophobia, impaired visual accommodation, and dryness of the mouth. Frequently gastrointestinal motility is disturbed, producing either diarrhoea or constipation, and paralytic ileus is not uncommon. In the present case it is interesting that actual paralysis occurred, presumably a quantitative effect.

Tetramine (teramethylammonium hydroxide) produces typical curare-like effects in mammals and frogs. The vascular system shows a fall of blood pressure, with a slowing of the heart by peripheral vagus stimulation and peripheral vasomotor depression. Respiration is temporarily paralysed by intravenous injections of tetramine owing to a curare-like effect on the phrenic nerves. Some workers believe that the respiratory action is entirely central, with the primary stimulation followed by depression of the medullary centres (Sollmann, 1949). Excretion of tetramine is very rapid in mammals, which may account for the transient symptoms of food poisoning in mild cases.

Whelk poisoning is said to be a public health problem in Hokkaido, Japan, where numerous intoxications have occurred, but the details of these outbreaks are not known (Asano, 1952; Kanna and Hirai, 1956).

The common whelk (*Buccinum undatum*), which can grow to 6 in (15 cm) in length, is still eaten in some areas. This species is non-toxic unless, possibly, after feeding on mussels contaminated by *G. tamarensis*. The periwinkle (*Littorina littorea*) is another non-toxic species eaten in many parts of the United Kingdom. A recent survey in the Forth showed no exogenous toxin in samples taken at a time when high levels were recorded in mussels (Department of Agriculture and Fisheries (Scotland), 1969, 1970).

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