

## Letters to the Editor

### High dose atropine in organophosphorus poisoning

Sir,

We read with interest the report by Afzaal and colleagues<sup>1</sup> of a case of severe organophosphorus (OP) insecticide poisoning. Their patient received 3369 mg atropine over 8 days and the authors state that a dose of atropine as large as this has not previously been given for OP poisoning. However, a small number of patients do require massive quantities, in particular those severely poisoned with highly lipid soluble compounds, such as fenthion.<sup>2</sup> Total doses as high as 3911 mg,<sup>3</sup> 11,422 mg<sup>4</sup> and 19,500 mg<sup>5</sup> have been given in severe cases previously reported.

The clinical details given by Afzaal *et al.* are too brief to judge the reasons for prolonged high-dose atropine therapy, but bronchorrhoea is likely to have been the main major indication. Even so, peripheral antimuscarinic activity of atropine may not be the only antidotal property of the drug in OP poisoning, and additional specific antidotal effects on the central nervous system have been observed both in animals<sup>6</sup> and in man.<sup>7</sup>

Afzaal *et al.* conclude their report by asking 'why such a high dose of atropine was needed?' The explanation is likely to be two-fold: (i) the patient was severely poisoned, and (ii) inadequate doses of pralidoxime were administered. Consideration of the mechanism(s) of OP toxicity leads us to believe that it is necessary to continue pralidoxime for as long as the OP compound or its active metabolite are present in the body. Thus, the use of pralidoxime for only a few hours or at most one or two days, as recommended in many texts, is unlikely to be effective in very severe cases such as that reported by Afzaal *et al.*

It is generally accepted that plasma pralidoxime concentrations of 4 mg/l are necessary to achieve a satisfactory therapeutic effect. This suggestion is based on experiments in anaesthetized cats given lethal doses of intravenous sarin,<sup>8</sup> plasma pralidoxime concentrations of 4 mg/l were required to counteract neuromuscular block, bradycardia, hypotension and respiratory failure. More recent studies support this conclusion,<sup>9,10</sup> but measurement of plasma pralidoxime concentrations is rarely available in clinical centres. To achieve plasma pralidoxime concentrations of 4 mg/l, we therefore recommend<sup>11</sup> that pralidoxime methanesulphonate (P<sub>2</sub>S) or chloride should be administered in doses of 30 mg/kg body weight intravenously every 4 or 6 hours, respectively, until full recovery occurs. Thus, the average adult will require approximately 8–12 g of oxime daily (depending on the salt employed), for as long as the patient exhibits the feature of poisoning.

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The contents of this letter represent the authors' views alone and in no way commit the Department of Health.

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### Common bile duct gallstones; anicteric presentation in the elderly – under-recognized but important

Sir,

Common bile duct (CBD) stones usually present with jaundice even in the elderly.<sup>1</sup> However, the absence of jaundice should not deter clinicians from considering a diagnosis of CBD stones. To highlight this we report three elderly women who presented with vague symptoms and abnormal liver function tests but without hyperbilirubinaemia. All three were found to have CBD stones and after their removal the symptoms and abnormal liver function resolved.

Case 1 – An 84 year old woman with a 2-month history of intermittent upper abdominal discomfort, anorexia and nausea. On examination she was agitated and confused. Full blood count and biochemical profile were normal except for a raised alkaline phosphatase (286 IU/l; normal 30–120). Abdominal ultrasound showed dilatation of the CBD. Endoscopic cholangiography (ERC) demonstrated a single large CBD stone which was removed after endoscopic sphincterotomy.

Case 2 – An 84 year old woman with recurrent episodes of abdominal pain accompanied by a confusion. Biochemical profile was normal except for a raised alkaline phosphatase of 499 IU/l and aspartate aminotransferase of 52 IU/l (normal 0–40). Abdominal ultrasound showed

a dilated CBD (1.2 cm) but no duct stones were seen. ERC showed several CBD stones which were removed following endoscopic sphincterotomy.

Case 3 – A 77 year old woman with a 4-week history of diffuse abdominal discomfort, nausea and vomiting, and had also had a rigor. The only abnormal finding was a temperature of 38.2°C. Biochemical profile showed an alkaline phosphatase of 582 IU/l and an aspartate aminotransferase of 119 IU/l. Abdominal ultrasound showed a dilated CBD (1.4 cm) and ERC demonstrated a large CBD stone which required surgical removal.

These three cases emphasize that CBD stones can, in the elderly, cause considerable morbidity without jaundice. CBD stones may present with rather vague non-specific symptoms and laboratory investigations. Before attributing these to other causes, a history of cholangitis should be sought and, even in the absence of jaundice, CBD stones excluded.

Abdominal ultrasound is a useful non-invasive test which quite reliably detects CBD dilatation but may fail to identify to CBD stones themselves. Cholangiography should be performed and ERC has advantages over percutaneous cholangiography since it can be combined with endoscopic therapy. When CBD stones cannot be removed endoscopically we recommend surgical removal.

Jones *et al.* noted the importance of investigating elderly patients with isolated elevation of alkaline phosphatase; they reported the cases of four women with underlying biliary disease.<sup>2</sup> The cases we present are similar in their biochemical findings, absence of jaundice and non-specific symptomatology. So, a raised alkaline phosphatase may be the sole liver function test abnormality in patients with CBD stones and before attributing this to Paget's disease we recommend investigating the biliary tree. All the patients showed a gratifying improvement following clearance of their common bile duct stones.

In summary, biliary stones are common in the elderly and may present with non-specific symptoms, and in the absence of jaundice diagnosis may be delayed. With increasing numbers of elderly patients this anicteric presentation of gallstones merits wider recognition.

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#### Coexistent multiple myeloma and MEN type 1

Sir,  
Primary hyperparathyroidism and other endocrine tumours are occasionally associated to constitute well

defined syndromes (multiple endocrine neoplasia – MEN – syndromes, type 1 and type 2). Furthermore, recent studies seem to suggest an increased risk of developing a malignant disease in patients with primary hyperparathyroidism.<sup>1</sup>

We here report the case of a 70 year old white woman who presented with clinical features consistent with acromegaly. The clinical diagnosis was confirmed by the finding of raised serum growth hormone levels in basal conditions (15 ng/ml; normal values lower than 10 ng/ml) that increased following thyrotrophin releasing hormone (TRH) administration.

The patient had undergone surgery for primary hyperparathyroidism due to a parathyroid adenoma in 1979; the diagnosis was confirmed both by the histological examination (biopsy of another gland showing normal appearance) and the occurrence of tetany after parathyroidectomy. During this hospitalization, serum protein electrophoresis showed a low  $\gamma$ -globulin monoclonal peak, this finding being relatively common in patients with primary hyperparathyroidism. However, unlike other reports<sup>2</sup> this monoclonal band did not disappear following surgery. Laboratory tests showed an increase of this abnormal peak in the following years. A multiple myeloma was therefore diagnosed in 1988 based on the presence of a serum monoclonal paraprotein and bone marrow aspiration. The patient is therefore undergoing therapeutic courses with both steroidal and chemotherapeutic agents.

Previous papers have reported the rare association between primary hyperparathyroidism and multiple myeloma and between myeloma and acromegaly; on the contrary, to our knowledge, there is no paper describing the association of sporadic MEN type 1 and multiple myeloma in the same subject.

Although we cannot exclude that all three diseases might have associated in our patient by chance, we can also suppose that a common aetiological factor could link them by inducing neoplastic transformation of different cell lines. With regard to this hypothesis it must be stressed that, in animal experiments, the expression of a specific viral oncogene able to transform most cell types, results in the preferential phenotypic development of multiple endocrine tumours or, at least, in proliferative disorders of other neuroendocrine cells.<sup>3</sup> Furthermore, a humoral factor that can stimulate parathyroid cell growth *in vitro* and, possibly, other endocrine cells has been recently discovered in patients with MEN type 1.<sup>4</sup>

It can also be hypothesized that among the disorders we observed only one constitutes the primary event secondarily inducing the others. Increased serum calcium levels related to hyperparathyroidism might be the primary cause, according to some studies which demonstrate that calcium acts as a mitogenic factor for some cell lines '*in vitro*'.<sup>5</sup> Alternatively the myelomatous proteins might interfere with polypeptide hormone synthesis, and/or bind their circulating fractions, and/or block their peripheral effects; these events might secondarily stimulate both parathyroid and hypophyseal secretory activity.<sup>6</sup>

Finally, it can be also speculated that persistently high growth hormone levels could stimulate cellular proliferation: a higher incidence of acute leukaemia has, in fact, been demonstrated in patients treated with synthetic growth hormone for a long time.<sup>7</sup>