in these studies ranged from morphine 12 mg/24 hours to papaveretum 72 mg/24 hours. Various protocols were used, but we were unaware of any double blind study used to test this hypothesis. Our study was performed double blind with a dose of 31.6 (5.1) mg given over 24 hours. An identical procedure (cholecystectomy) was performed in all patients so that the stress caused by having an operation was similar for both the treated and control groups.

The degree of pain experienced after operation was similar in both groups throughout the study (table III and figure).

TABLE III—Pain scores after operation. (Values are numbers (%) of total measurements)

Pain score*	Group given morphine infusion (85 measurements)	Control group (65 measurements)
0	20 (24)	15 (23)
1	30 (35)	25 (39)
2	25 (29)	18 (28)
3	10 (12)	7 (11)

*All differences between groups not significant.

Despite a bolus dose of morphine 10 mg one hour before induction and a second dose during induction, pain was worse immediately postoperatively (figure). The total abolition of pain by the use of narcotic analgesics may be undesirable because of the risk of respiratory depression. In this study, however, neither method achieved a satisfactory degree of analgesia as only a quarter of the measurements of pain were pain score 0. Over a third of the measurements of pain were considered to be excessive—that is, moderate or severe pain scores. The results therefore fail to substantiate the claim that continuous infusion of morphine produces better relief of pain.

Continuous infusion also failed to reduce the dose of morphine required. In addition to the fixed dose during continuous infusion, intramuscular morphine was given as required for pain; the dose delivered therefore was roughly titrated against pain. Both groups received similar amounts of intramuscular morphine during the first 24 hours. This resulted in the group who were given infusions of morphine having a significantly greater total cumulative dose of morphine (intramuscular plus

intravenous) during the first 24 hours ($p < 0.002$). During the second 24 hour period, however, after the respective intravenous infusions were withdrawn the group who had received infusions of morphine required significantly more morphine by intramuscular injection than the control group. The patients who had had infusions of morphine may have developed tolerance to morphine due to the significantly greater dose that they received during the first 24 hours.

Endogenous enkephalins, particularly β endorphin, are promoted by stress caused by operations¹⁰ and thought to represent an endogenous analgesic system.¹¹ Opiates act on endorphin receptors and produce analgesia.¹² Administration of intravenous morphine by infusion postoperatively causes a noticeable decrease in the plasma concentration of β endorphin.¹⁰ We hypothesise that the apparent tolerance shown by patients who received infusions of morphine may have been due to depression of the β endorphin system by the large dose of morphine received during the first 24 hours.

In conclusion, intravenous infusion of morphine at the dose used in this study failed to reduce the degree of pain beyond that which would require the prescription of morphine by intramuscular injection, and patients receiving morphine infusions appeared to have more side effects.

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SHORT REPORTS

Intravascular haemolysis induced by pentachlorophenol

Pentachlorophenol is a potent insecticide, fungicide, bactericide, and herbicide. It is soluble in water and organic solvents and is well absorbed through the skin, by ingestion, and by inhalation. Because of its toxicity strict precautionary measures should be taken when it is used, including wearing protective clothing and ensuring that the hands and face are well covered.¹⁻³ We report on a patient who developed intravascular haemolysis after negligent use of pentachlorophenol. To the best of our knowledge intravascular haemolysis has not previously been described as a side effect of this insecticide.

Case report

A 56 year old, previously healthy woman was admitted to our department for investigation of excessive weakness, palpitation, nausea, sweating, and systemic fever. The day before she had used an insecticide containing pentachlorophenol to clean wooden furniture. She had handled the solution and inhaled its vapour without taking any precautions.

On examination she seemed well, but pronounced pallor and mild jaundice were observed. The heart rate was 100 beats/min, blood pressure 100/

70 mm Hg, and temperature 39°C; the rest of the examination yielded normal results. The haemoglobin concentration was 7 g/dl, reticulocyte count 12%, and white cell count $8.1 \times 10^9/l$ with a shift to the left. A peripheral blood smear showed microcytosis, spherocytosis, and anisocytosis. The haptoglobin concentration was reduced, bilirubin concentration 62 $\mu\text{mol/l}$ (3.6 mg/100 ml) (indirect), and lactate dehydrogenase activity 414 IU.

During the first two days after admission she complained of excessive weakness, and the haemoglobin concentration dropped to 5.3 g/dl. She was given two units of red blood cells, and her haemoglobin concentration rose to 9.0 g/dl. Five days after admission a gradual improvement occurred paralleled by resolution of the fever, tachycardia, palpitation, and jaundice. Reticulocytosis (up to 30%) was noticed, but the haptoglobin and bilirubin concentrations and lactate dehydrogenase activity returned to normal. She was discharged two weeks later. Six months later her symptoms had not recurred.

Comment

This patient presented with intravascular haemolytic anaemia, and direct toxic injury with pentachlorophenol was postulated. There are many reports on the toxicity of pentachlorophenol, including cases with fatal outcomes.¹⁻⁴ Acute toxicity causes fever, sweating, tachycardia, tachypnoea, and pronounced generalised weakness; other features include headache, dizziness, nausea, and shock leading to

death.¹⁻³ Pharmacokinetic studies in monkeys showed that the half life of pentachlorophenol is 72-83 hours.⁵ Eighty per cent of the substance is excreted in the urine, and the remaining 20% is detoxified by the liver.²

The basis of pentachlorophenol toxicity is the ability of the substance to interfere with oxidative phosphorylation in cells.² Storage of energy in the form of adenosine triphosphate is prevented, leading to a compensatory increase in the basal metabolic rate which is responsible for most of the principal clinical features of pentachlorophenol toxicity.^{1,2}

The main source of energy in red blood cells is anaerobic glycolysis; energy is stored in molecules of adenosine triphosphate, a process that might be prevented by the toxic effects of pentachlorophenol. During shortage of energy red blood cells cannot continue performing their vital functions like preserving the osmotic equilibrium across the cell membrane, the cation pump, and cell deformability. This metabolic handicap may lead to premature lysis of the cells. We suggest that pentachlorophenol acts by blocking the formation of adenosine triphosphate leading to haemolysis. We recommend, therefore, that precautions are taken when using this potent and widely used chemical to avoid this possible complication.

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Changes in serum thiocyanate concentration on stopping smoking

The serum thiocyanate concentration is one of several variables used to substantiate the extent of exposure to tobacco smoke in smokers.¹ Thiocyanate is used because of its comparatively long biological half life, which is generally considered to be two weeks. This figure is based on the findings of Pettigrew and Fell,² who measured serial thiocyanate concentrations at fairly long intervals in one person who had stopped smoking. I performed a similar study in six subjects to obtain a more exact determination of the half life of thiocyanate and a more precise description of the thiocyanate concentration curve.

Subjects, methods, and results

Three healthy men and three healthy women who had smoked cigarettes for from six to 20 years stopped smoking completely. The initial concentration of thiocyanate was determined once within five days before they stopped smoking. After they stopped smoking four or five fasting specimens of blood were taken from each of the subjects, with the last samples being taken 26, 30, 35, 38, 39, and 44 days after they stopped. The samples were obtained in the morning at fixed times for each person with the subjects sitting. A tourniquet was applied for a maximum of one minute and removed after insertion of the needle. Specimens were drawn into Vacutainers (Becton and Dickinson) and centrifuged after 45 minutes. The resulting serum was divided into two aliquots, one of which was analysed that day. The other was kept at -50°C for serial analysis until all the specimens had been taken from that particular subject. Thiocyanate concentrations were analysed according to the method described by Butts *et al.*,³ which was modified for use with a Technicon SMA 12/60 Auto-Analyzer.⁴ Storage of the specimens did not affect the result, and so the serial measurements that showed the smaller methodological error were used for evaluation.

The figure shows the changes in thiocyanate concentrations in all subjects. The time at which half of the difference between the initial and final values (smoking and non-smoking values) is reached is considered to be the half life. The absolute values initially and finally were 130 and 52, 148 and 69, 155 and 54, 155 and 48, 146 and 25, and 186 and 46 µmol/l. The biological half life of thiocyanate was determined to be 6.4 (SD 0.9) days.

Comment

In epidemiological studies data on smoking obtained by questionnaire are increasingly being found to be insufficient, and objective measurements of the true exposure to smoke are needed.⁵ This requires, however, a more detailed knowledge of the properties of these "objective indicators." One such property is the half life of biological variables.

The mean biological half life of thiocyanate found in this study (about six days) is considerably lower than the value of about 14 days determined by Pettigrew and Fell, who measured the thiocyanate concentration one, three, four, five, and six weeks after their patient stopped smoking.² These relatively long intervals between measurements, in particular during the first three weeks, and the fact that only one subject was studied should be considered in assessing the reliability of this longer value for the half life of thiocyanate. The

Changes in serum thiocyanate concentrations in six subjects after they stopped smoking. Initial and final concentrations (smoking and non-smoking values) were plotted as 100% and 0% respectively.

standard deviation of about one day in the range of values near the half life (50%) is relatively small. Towards non-smoking concentrations (0%), however, values were considerably dispersed, which is not uncommon with biological variables of this type.

In my study I considered the thiocyanate concentrations 26-44 days after smoking was stopped to be non-smoking values. This would appear to be justified as a median thiocyanate concentration of 51 µmol/l was found in a cohort of non-smokers.¹

The biological half life of thiocyanate (six days) by far exceeds that of nicotine (30 minutes), cotinine (30 hours), and carboxyhaemoglobin (four hours).

The results of this study refer to cigarette smokers. On the basis of comparative measurements conducted previously,⁴ similar results can be expected in people who smoke cigars and pipes.

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