crushed to produce a morphine sulphate extract. He had increased his use from low dose to 300-400 mg daily.

Case 2—A 20 year old man presented to this unit with a seven month history of heroin misuse. He had injected heroin daily for four months and had subsequently inhaled it. For three weeks before presentation he had been injecting an extract of 100 mg slow release morphine sulphate tablets daily.

Case 3—A woman aged 26 presented with a long history of intravenous use of heroin. After treatment she had been free of drugs for one year. Inoperable carcinoma of the cervix was then diagnosed, and she was given slow release morphine sulphate (60 mg three times a day) for abdominal pain. The tumour was successfully treated with radiotherapy, but her use of slow release morphine sulphate tablets increased to 240 mg a day. She started extracting morphine from the tablets and injected it intravenously eight to 12 times a day.

Amount of morphine sulphate (mg) extracted from 60 mg tablets of slow release morphine sulphate by five inexperienced volunteers

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<tbody>
<tr>
<td>First attempt</td>
<td>36-52</td>
<td>45-38</td>
<td>49-32</td>
<td>37-82</td>
</tr>
<tr>
<td>Second attempt</td>
<td>22-42</td>
<td>44-30</td>
<td>45-56</td>
<td>36-08</td>
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With the cooperation of someone who had used slow release morphine sulphate tablets we recorded the extraction procedure on videotape. The recording was used to guide three nursing staff and two medical students with no previous experience of the extraction method in preparing two extracts from 60 mg tablets of slow release morphine sulphate. The subjects used procedures and equipment identical with those shown in the recording to reproduce “street” conditions as closely as possible. The extracts were analysed for morphine sulphate by high performance liquid chromatography.

The table shows the results of the extraction procedure. The subjects produced an extract with a mean content of 38.92 mg (range 22.42-49.32 mg)—that is, 65% of the available morphine sulphate. One sample was subjected to a second extraction (users often reprocess the residue from the original extraction) and this produced 15% increase in the amount of morphine sulphate.

Comment

Slow release morphine sulphate can be misused intravenously, and the three patients reported on had a high intake of heroin in a short time. Our results suggest that intravenous users manage to extract 65% of the available morphine sulphate and the dose of methadone prescribed for detoxification should be based on this figure.

Increasing misuse of prescribed drugs for intravenous use has been reported with temazepam, buprenorphine, and cyclizine.2 3 Sokol et al suggested that the formulation of a drug affects its potential for abuse and that prescribers have an obligation to consider this.1 Buprenorphine is now a controlled drug, and two manufacturers of temazepam have stopped making injectable preparations. We emphasise the need for caution when prescribing opiates of any form and the importance of checking whether a patient has a history of drug misuse before prescribing drugs that may be misused.

We thank Mr K Hale of the Regional Laboratory for Toxicology, Birmingham, for analysing the extracts of morphine sulphate.


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Spontaneous remission of hepatocellular carcinoma after massive gastrointestinal haemorrhage

G Toci, A Conte, P Guarascio, G Visco

Spontaneous remission of hepatocellular carcinoma is extremely rare.1 We describe spontaneous remission of hepatocellular carcinoma after a massive intercurrent gastrointestinal haemorrhage.

Case report

A 79 year old man had been attending our outpatient clinic since January 1980 with active liver cirrhosis secondary to non-A, non-B hepatitis. He received immunosuppressive treatment with prednisone (7-5 mg daily) and azathioprine (50 mg daily) from January to March 1980; the treatment was then altered to azathioprine alone (100 mg daily) because of gastric discomfort. All treatment was stopped in March 1983 after a second liver biopsy showed an increase in the histological signs of activity.

In June 1984 routine periodic radioimmunoassay showed an increased serum concentration of α fetoprotein (100 μg/l). Ultrasonography and computed tomography of the liver showed a round dense image, which was about 5 cm in diameter and had a necrotic core near the hepatic hilum. A liver biopsy guided by ultrasonography disclosed a microtrabeular hepatocarcinoma. His general condition deteriorated during the following months; he developed jaundice, and the serum concentration of α fetoprotein increased to 625 μg/l. No treatment was attempted because of his explicit, informed refusal.

In September 1984 his general condition deteriorated further and he was admitted to another hospital, where treatment with high doses of intravenous hydrocortisone (2 g daily) was begun. A few days later he had a massive haematatemesis followed by severe and prolonged shock. His haemoglobin concentration fell below 40 g/l for several hours, and endoscopy disclosed a bleeding gastric ulcer. He recovered from shock after the transfusion of 3 litres of fresh blood. His condition subsequently improved and his jaundice receded. Five months later ultrasonography of the liver showed a surprising reduction in the size of the tumour. In addition, his serum concentration of α fetoprotein had fallen to 165 μg/l.

Ultrasoundography and computed tomography in May 1985 showed a further reduction in the size of the tumour, and his serum α fetoprotein concentration was normal (5 μg/l). The tumour had completely disappeared by early 1987, and this was confirmed by computed tomography in 1988. Microlcalfcations were observed at the former site of the tumour.
Coffee consumption as trigger for insulin dependent diabetes mellitus in childhood

Jaakko Tuomilehto, Eva Tuomilehto-Wolf, Esa Virtala, Ronald LaPorte

Exposure to a risk factor is required to convert the HLA linked genetic susceptibility for insulin dependent diabetes mellitus into overt disease. The risk factors are not known: viruses, toxic chemicals, and certain dietary factors have been implicated, but results of studies have been unconvincing. A long prodromal period is commonly agreed to occur before the clinical symptoms of diabetes develop, and it has been postulated that the first exposure to a risk factor might happen before birth, even at the time of conception.

Finland has the highest incidence of insulin dependent diabetes in the world. The incidence has considerably increased during recent years as has the consumption of coffee. Finland now has the highest coffee consumption per person in the world. We investigated whether the well documented geographic variation in the incidence of insulin dependent diabetes could be attributed to differences in coffee consumption.

Methods and results

Data on the incidence of diabetes in various countries were mainly derived from the Diabetes Epidemiology Research International Study Group, and the national coffee consumptions per person were obtained from the International Coffee Organisation. The figure shows the association between the annual average national coffee consumption per person and the age standardised incidence of insulin dependent diabetes (age group 0-14 years). The simple correlation between coffee consumption and the incidence of insulin dependent diabetes was 0.74. A linear regression analysis showed that 53% of the geographic variation in incidence could be attributed to differences in coffee consumption. The countries with the highest coffee consumption per head also had the highest incidence of insulin dependent diabetes.

Comment

Exposure to a risk factor that triggers insulin dependent diabetes may occur before birth. For example, rubella infections during pregnancy are associated with an increased risk of diabetes in the child. Caffeine, the most widely used psychotropic agent, could also be a risk factor in utero for insulin dependent diabetes. Its half-life is prolonged in pregnancy, and it is known to cross the placenta into the fetus, where it may cause unwanted effects. It accumulates in fetal tissues, especially the liver and brain. It can also increase blood glucose concentrations in caffeine naive people. We postulate that high concentrations of caffeine or its metabolites have a toxic effect on intrauterine development of the pancreatic cells that produce insulin in genetically susceptible fetuses.

Pregnant women who consume large quantities of coffee have an increased risk of spontaneous abortions, premature deliveries, and giving birth to infants with reduced birth weights. Newborn babies eliminate caffeine remarkably slowly as they lack the enzymes that demethylate it. One case report suggested that hyperglycaemia occurred as a toxic effect in a 12 month old child who accidentally took 1-0-1-5 g caffeine. Caffeine is metabolised through the hepatic oxidation system, which is responsible for most drug oxidation reactions. The urinary excretion rate of 5-acetyl-6-formylaminoo-3-methyluracil, a metabolite of caffeine, strongly correlates with the reported rate of polymorphism in the N-acetylation of sulphonamides and

Subsequent three monthly follow up established that his recovery was complete.

Comment

Hepatocellular carcinoma is a frequent complication of liver cirrhosis, and patients usually die from gastrointestinal bleeding, cachexia, or liver failure. The clinical healing of our patient's hepatocellular carcinoma may have been related to the severe haemorrhagic shock. Because of its high metabolic requirements neutoplastic tissue is more sensitive than normal tissue to a sudden reduction of the blood and oxygen supply.

The liver receives a dual blood supply from the hepatic artery and the portal vein, whereas hepatomas are fed predominantly by the hepatic artery. Surgical procedures such as transcatheater arterial chemoembolisation and ligation of the hepatic artery branch have therefore been proposed to induce anoxia of the tumour when hepatectomy cannot be performed. The haemorrhage probably produced optimal conditions to kill neoplastic cells without damaging normal tissues. The sensitivity of hepatocellular carcinoma to a reduction in blood supply would therefore seem to be confirmed by this case history.

Coffee consumption as trigger for insulin dependent diabetes mellitus in childhood

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