Fasting venous blood was collected at 9 am into cooled heparinised tubes and centrifuged immediately, the plasma being stored at $-20°C$ until assay. Calcitonin was measured in the plasma by direct immunoassay[5] (five days of incubation) with a detection limit of 6·0 pg/tube and an intra-assay variation of under 10%. All samples were assayed at the same time. Statistical evaluation was with the χ^2 test for variables with large numbers of undetectable values and the correlation calculated with Spearman's correlation coefficient.
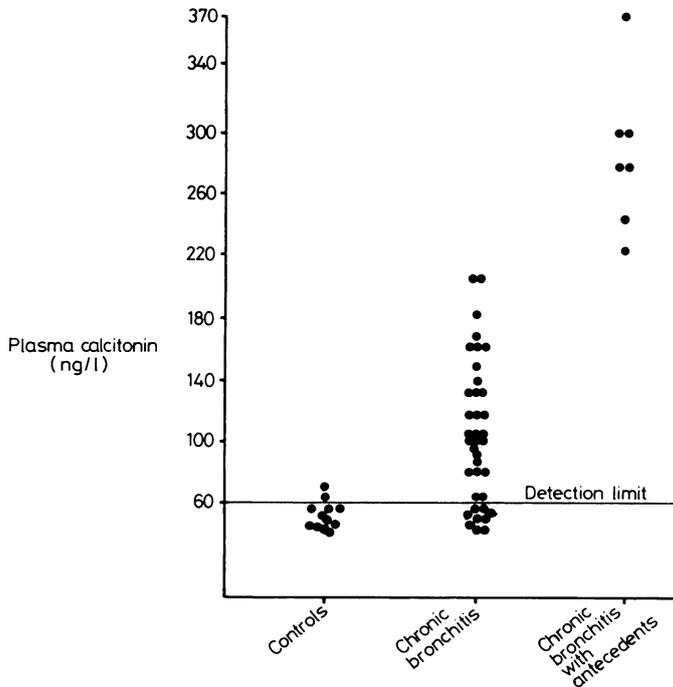
Plasma calcitonin concentrations in controls, patients with chronic bronchitis, and patients with chronic bronchitis and familiar antecedents of chronic bronchitis or lung cancer.

Of the 45 patients, 34 had plasma calcitonin concentrations above the highest value (80 ng/l) recorded in the controls (p < 0·001; fig). There was no correlation between the plasma calcitonin concentrations and total numbers of cigarettes smoked during life (r = 0·239; p > 0·05), nor was there a significant difference in concentrations between patients who had given up smoking and those who had carried on (p > 0·05). A subgroup of seven patients found to have familiar antecedents of chronic bronchitis or lung cancer had the highest plasma calcitonin concentrations recorded in the study (>220 ng/l; fig).

Comment

In mammals and submammalian vertebrates the main sources of calcitonin are the thyroid and ultimobranchial gland, respectively; in lizards, however, calcitonin is isolated from lung.[2] Immunochemical studies have also shown a calcitonin-like material in lizard lung and in bronchial and bronchiolar Kulchitsky cells of man.[2 3]

In our study patients with chronic mucopurulent bronchitis had significantly increased plasma calcitonin concentrations. Whether such high values occur in simple and obstructive chronic bronchitis remains to be determined. That the subgroup of patients with familiar antecedents of chronic bronchitis or lung cancer had the highest concentrations suggests that calcitonin is derived from Kulchitsky cells, since these might increase or be overactive in such patients. Confirmation, however, must await a larger series.

In conclusion we think that the high plasma calcitonin concentrations found in lung cancer may, at least in some cases, be partially due to the chronic bronchitis that so often accompanies the tumour.

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Severe metabolic acidosis early in paracetamol poisoning

Serious effects of paracetamol poisoning are held to become evident days after ingestion. We report serious toxicity presenting within hours.

Case report

A 56-year-old housewife swallowed about 75 g of paracetamol. She was admitted 11 hours later deeply unconscious. Examination showed diminished corneal reflexes, absent pain and oculocephalic responses, pallor, vomit around the mouth, tachypnoea, clear chest, trismus, arm flexor spasm, leg flaccidity, and generalised areflexia. Her pulse was irregular (104/min), and blood pressure 110/60 mm Hg with good peripheral perfusion. Stomach washout was performed. Initial assessment included an electrocardiogram, which showed multifocal ventricular extrasystoles and runs of ventricular tachycardia which were abolished by lignocaine. Arterial pH at 12 hours was 6·9, base deficit 25·2, Po_2 16·3 kPa (123·0 mm Hg), Pco_2 2·5 kPa (18·8 mm Hg), and standard bicarbonate concentration 5·1 mmol (mEq)/l (blood gas analyser). Ketostix result was negative and anion gap 34 mmol (mEq), and arterial lactate concentration was 12·9 mmol/l (116·0 mg/100 ml) (normal < 1·2 mmol/l; < 10·8 mg/100 ml).

Rapid infusion of 300 mmol bicarbonate raised the arterial pH to 7·29. Thereafter bicarbonate was infused slowly. By 21 hours after ingestion her acid base state was normal. Plasma paracetamol concentration at 11½ hours was grossly raised at 959 mg/l (estimated half life 11 hours). N-acetylcysteine infusion was begun 13 hours after ingestion and followed a standard regimen.[1] Charcoal haemoperfusion was instituted at 14½ hours and continued for eight and a half hours (see table). A total of 22·8 g of glucuronide and sulphate derivatives of paracetamol plus free paracetamol was excreted in the urine between 12 and 23 hours after ingestion. Screening showed no other drugs. Consciousness gradually returned, and at 24 hours she was fully alert. After the overdose her blood sugar concentration was raised but seven days later the glucose tolerance curve was normal. The liver was only mildly damaged with a peak serum aspartate transaminase value of 258 IU/l at 23 hours and a maximum prothrombin time of 19 s.

Changes in plasma paracetamol concentrations with time after ingestion.

Time (hours)	11½	12½	16	17	18	19	20	21	22	23
Paracetamol (mg/l)	959	918	555	394	288	206	155	144	100	67

Comment

The profound acidosis in this patient may have been attributable to type B lactic acidosis. Neither lactic acidosis nor severe acid base disturbance is recorded in the early stages after paracetamol poisoning. Record et al[2] found metabolic acidosis in four out of 28 patients who developed fulminant hepatic failure. In three cases this occurred after paracetamol ingestion, was severe and attributed to lactic

acidosis, but preceded clinical hepatic failure. Unlike our patient, however, they were seen 48 hours after ingestion and also had circulatory disturbance and hypoglycaemia.

Loss of consciousness early with paracetamol alone is not recognised; however, profound lactic acidosis from whatever cause may be associated with coma. In our patient rapid correction of the acid base state produced only slight improvement in conscious level.

Dixon[3] proposed paracetamol poisoning as a cause of sudden death before histological hepatic damage. The ventricular arrhythmias possibly due to the acidosis noted in this case could provide a mechanism.

Plasma paracetamol concentrations of the magnitude recorded here would normally be expected to cause hepatic failure.[4] Remarkably only minor hepatic damage occurred. Evidence suggests that intravenous acetylcysteine offers maximum advantage when given within eight hours after ingestion.[1] In our patient drug absorption may have been delayed or perhaps severe acidosis interfered with the mechanism associated with toxicity. In such circumstances acetylcysteine may be of more than anticipated benefit. In late treatment (10-24 hours) Winchester et al[5] suggested that both acetylcysteine and haemoperfusion are of value in offsetting hepatotoxicity. This case supports their view.

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Effect of two hypnotic drugs on actual driving performance next morning

Most drugs that affect the central nervous system impair driving, at least temporarily.[1] [2] Furthermore, many hypnotic drugs of the benzodiazepine group have some "hangover" effects next morning and have been shown to impair performance in (experimental) psychomotor tasks, though the degree of impairment depends on the dose of the hypnotic, its plasma half life, and individual variability.[3] Such impairment is taken to mean that morning driving might be impaired: but is it? We could find no evidence that other workers had looked at the effect of these drugs on actual driving so we decided to do so. We chose a drug with a relatively short half life, temazepam, and one with a longer one, flurazepam.

Methods and results

Twelve professional women were recruited (women more often take hypnotics than men). All were fit and well, drove regularly, and had passed their driving tests at least two years before. All gave informed consent and avoided other drugs and alcohol over the test period. Each subject served as her own control and took a single dose of either placebo, flurazepam 15 mg, or temazepam 20 mg in a balanced-order design (a double-placebo technique was used, as the temazepam and its placebo were in soft capsules). Doses were taken a week apart and, for each subject, at the same time of night. Exactly 12 hours later the subject arrived at the test centre, all tests being carried out between 9 and 11 am. After objective and subjective tests of arousal and mood (to be reported elsewhere) she walked to a nearby car park,

where the driving-test course was laid out. A standard Datsun saloon was used: none of the subjects had driven the particular model before. Two minutes' practice with the car over the course before testing was allowed for each subject.

Each subject drove three times over the first test course, a weaving task. She had to drive as fast as possible, weaving in and out between plastic bollards over a measured course, turn round, and come back to the starting point without hitting any of the bollards. Subjects were told there were financial penalties for going too slowly or striking bollards. Note was made of the time taken to complete the test and of the number of bollards hit. The second test was a gap-acceptance task, in which the subject drove 10 times round a circular course: at one part of the course she was presented with a gap formed by two bollards (the width between them was varied each time by the experimenters), and at 30 m she had to decide instantly whether the gap was wide enough to drive through (in which case she did so) or too narrow (in which case she drove past it). Note was made of the time taken to complete the whole task, the number of passable and non-passable gaps attempted or rejected, and the number of hits occurring while passable gaps were negotiated. Both tests were similar to tasks in other driving experiments.[1] [2] [4] Results were analysed using appropriate non-parametric statistical techniques.[5]

After taking flurazepam subjects hit significantly more bollards in the first test than under placebo conditions (table). In the second test subjects taking both drugs hit the side of the passable gaps significantly more often than when taking placebo, without a concomitant increase in speed or decrease in ability to recognise a passable gap; this suggested carelessness rather than increased risk taking. Out of 144 possible non-passable gaps in the second test, only five were attempted.

Number of hits in two tests

	Weaving test: bollards hit	Gap test: "passable"* gaps hit in passing through
	Placebo	
Total	21 (36 attempts)	18 (72 attempts)
Mean	1.75 ± 2.14	1.5 ± 1.2
	Flurazepam	
Total	41† (36 attempts)	33‡ (72 attempts)
Mean	3.42 ± 2.9	2.75 ± 1.4
	Temazepam	
Total	29 (36 attempts)	35‡ (72 attempts)
Mean	2.4 ± 2.0	2.9 ± 1.4

*"Passable" gap was wider than car: all passable gaps attempted.
†Significantly more than placebo ($p < 0.05$; randomisation test).
‡Significantly more than placebo ($p < 0.025$; randomisation test).

Comment

A single night-time dose of both hypnotics caused changes in driving behaviour next morning that increased the chance of a road accident. Whether the effect wears off in the day (and if so, when), whether subjects adapt to repeated dosing, whether the effect is dose dependent, and whether men would be affected we cannot say; we suggest, however, that doctors should advise patients to avoid morning driving for the first few days of taking one of these hypnotics. The effect of temazepam was unexpected, as it has a short half life and has little effect on psychomotor tests the next morning[3]: the study should be replicated.

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