the hands, which was diagnosed by an employment medical adviser as endogenous eczema exacerbated by contact with quinalbarbitone sodium powder. The operatives routinely wore protective overalls and caps but no gloves or masks. To check whether possible systemic absorption of quinalbarbitone sodium by inhalation or skin contact was occurring blood samples were obtained from the six workers towards the end of the shift and analysed by specific ion mass spectrometry at the Health and Safety Executive Occupational Medicine and Hygiene Laboratories.

Blood quinalbarbitone sodium concentrations (table) approached those to be expected after an adult therapeutic dose, the highest being 3.9 µmol/l (93 µg/100 ml). For comparison single oral doses of 231 mg/70 kg body weight result, on average, in maximal blood concentrations of 8.4 µmol/l (200 µg/100 ml) after three hours.³ An adult oral dose of 100 mg quinalbarbitone sodium is sufficient to produce a hypnotic effect⁴ and, assuming a linear kinetic model, would produce a blood concentration of 4.2 µmol/l (100 µg/100 ml). Personal air samples from the breathing zones of six workers were analysed by high performance liquid chromatography; the mean concentration of quinalbarbitone sodium in the dust was 0.46 mg/m³ (range 0.08–1.49 mg/m³). Dust extraction was subsequently improved so that the highest concentration in the air samples fell to 0.36 mg/m³; operatives were also instructed to wear airline masks and surgical gloves. Despite these improvements we still detected quinalbarbitone sodium in blood samples taken towards the end of the shifts on two subsequent occasions (second and third surveys; table). Further discussions then disclosed that quinalbarbitone sodium powder regularly contaminated the home clothing worn beneath the protective overalls and that the wearing of gloves, but not airline masks, was being neglected. Skin contact with quinalbarbitone sodium powder had therefore continued to occur but further efforts to reduce exposure could not be made because the company had closed down.

Blood concentrations of quinalbarbitone in workers manufacturing capsules before and after measures to reduce exposure from inhalation of powder

	Before measures (first survey)	After measures	
		Second survey	Third survey
Blood concentration (µmol/l):			
Mean	1.7	1.0	0.6
Range	0.4–3.9	0.6–1.3	0.2–1.1
No of workers	6	4	6

Therapeutic blood concentration 4.2–8.4 µmol/l (100–200 µg/100 ml) (see text).
Conversion: SI to traditional units—Quinalbarbitone: 1 µmol/l ≈ 24 µg/100 ml.

Comment

In this plant exposure to quinalbarbitone sodium occurred initially through the inhalation of airborne powder during machine operation and filling of the hoppers as well as through skin contact. Wearing airline masks should have greatly reduced exposure from inhalation, but we surmised that skin contact had continued as a result of the airborne dust penetrating the protective overalls and from the failure to wear gloves regularly; the latter interfered with the fine hand movements required to handle the capsules. Despite the small number of operators available for study we concluded that substantial absorption of quinalbarbitone sodium was most likely to be occurring through the skin, a finding to be expected given that quinalbarbitone sodium is very lipid soluble⁴ but which to our knowledge has not been described before. Exposure may also have occurred by accidental ingestion of powder from contaminated hands, intentional self medication, or inadequate respiratory protection, but we considered that these were all less likely than skin absorption, which would have been overlooked if exposure had been assessed using dust in air alone.

The intermediate acting barbiturates such as quinalbarbitone sodium are still used as hypnotics in severe intractable insomnia and as sedatives in anxiety states. Although the workers were not apparently affected by the drug, repeated occupational exposure to barbiturates may place the fit worker at risk from adverse effects without any therapeutic advantage. These effects include tolerance and dependence, additive or synergistic interaction with other drugs or alcohol, induction of liver enzymes, and possible tumour promotion,⁴ though to our knowledge none of these has been reported in barbiturate workers. Increased proneness to accidents at work or elsewhere—for example, when driving—is also possible, especially if the workers are unaware that absorption of drug is occurring. Unlike barbiturates, very sensitive methods for measuring absorption are not available for most drugs, but our study shows the potential value of such testing in the occupational setting. In the United Kingdom exposure limits to airborne dust, but not biological limit values, have been set for only three drugs (aspirin, warfarin, and glyceryl trinitrate).⁵ Exposure limits for other drugs which address the problems of skin absorption, where applicable, are clearly needed.

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Synergism of spironolactone and lithium in mania

Plasma aldosterone concentrations are raised in manic patients.¹ Antagonism between aldosterone and lithium has been suggested because of their opposing effects on adenylyl cyclase.¹ The disorder in manic depression has also been attributed to altered membrane functioning through the action of aldosterone.² Moreover, endogenous aldosterone is active in the hypothalamus and may be localised there, as may spironolactone.² When six manic depressive patients were taken off lithium because of side effects spironolactone was substituted and follow up at one year showed that five of these patients were still in remission.²

It has been suggested that when diuretics, particularly thiazides, are used in conjunction with lithium, lithium toxicity may develop through hyponatraemia and excessive retention of lithium.^{3,4} A group of manic patients refractory to lithium at therapeutic serum concentrations were shown to become responsive, however, when lithium was combined with thiazides or a low sodium diet.⁵ The improvement of lithium action was not considered to be due only to the very small increases in serum lithium concentrations as many patients improved despite not having higher concentrations or in some cases having lower ones. Moreover, even when the lithium concentrations were raised during treatment with these combinations, if subsequently the dosage of lithium was increased without added thiazide or a low sodium diet patients did not show an equivalent improvement.⁵

Case report

A married, 42 year old woman had had recurrent manic illnesses over the past 15 years; for the past four years she had been maintained in remission with lithium alone (serum lithium concentrations 0.5–0.7 mmol(mEq)/l). During the past year she had suffered two manic relapses for which she had been treated in hospital elsewhere. During her first admission she received lithium, carbamazepine, and a course of electroconvulsive treatment and remained well for the next three months taking lithium alone. She was discharged after her second relapse taking verapamil, clonidine, and lithium and when seen two days later was found to be suffering from lithium toxicity (serum concentration 2 mmol/l). After inpatient treatment at a renal unit she was discharged on no medication. At this point she was admitted to a local hospital, where lithium was cautiously administered to a concentration of 0.68 mmol/l. Concurrently she was given spironolactone 100 mg a day; serum potassium concentrations were checked daily to prevent hyperkalaemia. Thioridazine 100 mg and promethazine 100 mg at night were given as necessary. Within 24 hours of starting the spironolactone she became deeply sedated. Because of possible synergism between lithium and spironolactone the lithium was stopped, although at this stage the lithium concentration was only 0.68 mmol/l. Over the next few days she became more alert, and she was discharged a week later in remission taking spironolactone 50 mg daily, thioridazine 100 mg at night, and promethazine 100 mg at night. Over the next four months the sedation at night was stopped but she continued to take spironolactone 50 mg; she remained well.

Comment

This case indicates that synergism may occur between lithium and spironolactone, which might be clinically useful in patients resistant to lithium or in whom low dose lithium is advisable. Moreover, this case also indicates that spironolactone alone may maintain a manic patient in remission. Further research is needed to assess the mode of action of spironolactone alone or in combination with lithium in the treatment of mania.

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Dentists, dental nurses, and brain tumours

There is some evidence to suggest that exogenous factors might be important in the origin of brain tumours.¹⁻³ We investigated the risk of intracranial tumours in several occupational groups in a research programme. In this report we present the risks of glioblastoma among dentists and dental nurses.

Subjects, methods, and results

Cohorts of dentists and dental nurses aged 20-64 were identified from the Swedish census of 1960, and people within these cohorts who had cancer were identified from a record linkage to the cancer register for the years 1961-79. There were 3454 male dentists, 1125 female dentists, and 4662 female dental nurses.

The histopathological classification showed that of the brain tumours (ICD 193-0) in the cohorts, 18 were glioblastomas (astrocytoma III-IV according to Kernohan and Sayre⁴), four gliomas (astrocytoma I-II), and six meningiomas. The observed numbers of cases of cancer were compared with the corresponding expected numbers, calculated from the cumulative incidences for all employed people and the numbers of dentists and dental nurses. Stratification was by age (five year age groups), sex, and county. The cumulative incidences were calculated as the proportion of the census population that was recorded in the cancer registry. The analysis was based on the standardised morbidity ratio—that

is, the ratio of the observed number of cases to the expected number—with 95% confidence limits.⁵ For comparison standardised morbidity ratios for physicians and nurses were also calculated.

The table shows that among dentists and dental nurses glioblastoma was about twice as common as expected. For glioma the standardised morbidity ratio for the entire study population was 1.8, although with a wide confidence interval, while for meningioma the standardised morbidity ratio was 1.3. For all tumours combined the standardised morbidity ratio was 1.0 or 1.1 for all the different groups. The standardised morbidity ratio for glioblastoma among physicians and nurses was estimated as 1.3 and 1.2, respectively, with unity well within the confidence intervals.

Comment

Although the 1960 census gave the number of people whose present occupation was as a dentist or dental nurse, it did not provide information on the duration or level of exposure to products used in dental work. There might also have been errors in the reporting or coding of occupations in the census. Thus we may have included in our study people with little or no exposure to products used in dental work which could lead to underestimation of the increased risk. For 17 of the 18 cases of glioblastoma we were able to locate and review the medical records and thus determined that all these patients had indeed been assigned the diagnosis of glioblastoma. The basis for the diagnosis was either biopsy or necropsy findings. We did not take into account deaths from competing causes, but although this might possibly differ between people in the dental profession and the general population it is unlikely to do so only in respect of glioblastoma. Random fluctuations might explain the observed excess risk, but against this must be set the consistency of the results, and, in particular, the similarity of the standard mortality ratio's for dentists and dental nurses and for male and female dentists.

In conclusion, we think it unlikely that the sources of error mentioned above or factors known to be related to glioblastoma explain the observed excess risk. Most probably the origin is some occupational factor common to dentists and dental nurses—for example, amalgam, chloroform, or radiography.

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Observed and expected numbers of tumours and standardised morbidity ratios among dentists and dental nurses*

Diagnosis and category	Observed No of tumours	Expected No of tumours	Standard morbidity ratio	95% Confidence limit
Glioblastoma (astrocytoma III-IV)	18	8.47	2.1	1.3-3.4
Dentists, male	9	4.56	2.0	0.9-3.7
Dentists, female	3	1.22	2.5	0.5-7.2
Dental nurses, female	6	2.69	2.2	0.8-4.9
Physicians	11	8.48	1.3	0.6-2.3
Nurses, female	23	19.36	1.2	0.8-1.8
Glioma (astrocytoma I-II)	4	2.20	1.8	0.5-4.7
Dentists, male	2	0.99	2.0	0.2-7.3
Dentists, female	0	0.24	0.0	0.0-15.4
Dental nurses, female	2	0.97	2.1	0.2-7.4
Meningioma	6	4.59	1.3	0.5-2.8
Dentists, male	4	1.56	2.6	0.7-6.6
Dentists, female	1	1.00	1.0	0.0-5.6
Dental nurses, female	1	2.03	0.5	0.0-2.7
All tumours	596	572.31	1.0	1.0-1.1
Dentists, male	288	276.20	1.0	0.9-1.2
Dentists, female	97	98.78	1.0	0.8-1.2
Dental nurses, female	211	197.33	1.1	0.9-1.2

*Glioma and meningioma controlled only for sex and age; other diagnoses controlled for sex, age, and county.