dosing. Urine was collected during 0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours after dosing. Ampicillin was assayed in serum and urine by a microbiological assay.3 Urine samples were also assayed for penicilloic acid.4 Results were analysed by a two-way analysis of variance. Significant differences between mean values were determined by Duncan's multiple range test as appropriate. 

Talampicillin was administered as Talpen tablets containing 250 mg talampicillin hydrochloride equivalent to 169 mg ampicillin free acid. Ampicillin was administered as Penbritin capsules containing 250 mg ampicillin free acid. The bioavailability profiles of mean serum ampicillin concentrations are shown in the figure. Talampicillin dosed to fasting subjects was rapidly absorbed and hydrolysed to give a mean peak serum ampicillin concentration of 4.65 μg/ml at 40 minutes after dosing. Ampicillin dosed to fasting subjects was less rapidly absorbed giving a significantly lower mean peak serum ampicillin concentration of 2.46 μg/ml at 90 minutes (P<0.01). 

The mean peak serum ampicillin concentration after dosing talampicillin to non-fasting subjects was 3.26 μg/ml and occurred at 60 minutes after dosing. The rate of availability and mean peak serum concentration of ampicillin after dosing talampicillin were lower than those after dosing talampicillin in the fasting state (P<0.01) but superior to those after dosing ampicillin in the fasting state (P<0.01). When ampicillin was dosed to non-fasting subjects a mean peak serum concentration of 1.46 μg/ml was achieved at two hours. These values are significantly lower than those observed after dosing with ampicillin in the fasting state or with talampicillin in the fasting or non-fasting states (P<0.01). By six hours after dosing the urinary excretion of ampicillin accounted for 64% and 62% of the dose of talampicillin administered in the fasting and non-fasting subjects respectively. For ampicillin the comparable values were 39% and 23% for the fasting and non-fasting states respectively. The greater excretion of penicilloic acid after dosing with talampicillin results from the greater bioavailability of ampicillin from Talpen, since the ratio of penicillin to penicilloic acid excreted is similar in each case. The cumulative excretion of penicillin plus penicilloic acid accounted for 91 and 92% of the dose of Talpen administered to fasting and non-fasting subjects, confirming almost complete absorption of talampicillin in both situations. After dosing with Penbritin the urinary excretion of ampicillin plus penicilloic acid amounted to only 60 and 41%, after dosing to fasting and non-fasting subjects respectively. 

Discussion 

This study has shown that talampicillin is well absorbed from the gastrointestinal tract and is both rapidly and completely hydrolysed to release ampicillin. It has also shown the biological availability of ampicillin from 250 mg Talpen tablets to be greater than that from 250 mg of ampicillin administered as Penbritin capsules. These results are in accordance with the observations of Leigh et al5 and Verbist.6 When dosing with ampicillin itself both the rate of absorption and total biological availability is adversely influenced by dosing in the presence of food. This is not so when dosing with talampicillin. Although the rate of absorption of talampicillin is influenced by dosing in the presence of food, total absorption is unimpaired. Since the cumulative urinary excretion of ampicillin and penicilloic acid is as high as 90% after dosing with talampicillin but is only 40-60% after dosing with ampicillin it may be concluded that at least 50% and possibly 80% of intact talampicillin is absorbed from the gastrointestinal tract. 

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Finger clubbing and a gliomla 

The stimulus to write this article came from a patient who had finger clubbing and a brain tumour, which was assumed to be a metastasis from a hidden bronchial carcinoma. As the report shows, this assumption was incorrect.

Case report 

The patient was a 52-year-old, right-handed, cigarette smoker who presented in October 1976 with a short-lived episode of dysphasia and several attacks of central chest pain. There were no persistent signs of a left cerebral hemisphere lesion, apart from mild EEG changes, and the EMI scan (computerised axial tomography) was normal. The ECG showed changes of acute anteroseptal myocardial infarction, but there were no other abnormal findings in the cardiovascular system. The result of general examination was normal apart from nail changes, which could be described as "early finger clubbing." During the next few weeks the patient developed a progressively worsening dysphasia and was admitted in December 1976. The abnormal physical signs were definite dysphasia, incomplete right homonymous field defect, and mild right hemiparesis with cortical sensory loss. The EMI scan and a carotid angiogram showed a large neoplastic lesion in the temporal lobe. The patient had obvious bilateral finger clubbing with loss of the nailfold angle, boggyness of the nail bed, and increased curvature of the nail. General examination showed normal findings, with no clinical evidence of cardiovascular, pulmonary, hepatic, alimentary, or endocrine disease. The normal findings on investigations were: chest x-ray film, sputum cytology, blood count, and liver function tests. 

The patient's condition was unchanged for two weeks; then rather quickly he became unconscious and died in coma. At necropsy the large left temporal tumour was found to be a glioma. The rest of the body organs were examined carefully and the only abnormalities were a myocardial infarction and numerous calcified areas on the surface of the liver, which were histologically fibrotic and inactive. Each bronchus and lung segment were examined and no pathological process was found.

Comment 

The finger clubbing had clearly developed in two months and none of the recognised causes of clubbing was found despite a careful postmortem study.1 2 The fibrotic liver lesions were years old and
Brain rhythm that correlates with obesity

There is a strong correlation between an adult’s body weight and usual amount of REM (rapid eye movement) (paradoxical) sleep.1, 2 We now report a connection between the degree of obesity and the frequency of an ultradian brain rhythm here measured during sleep but also present by day.3 Sleep is categorised into two types, REM and NREM (non-rapid eye movement) (or orthodox), which alternate as sleep progresses. A cycle is made up of one period of NREM sleep plus an adjacent period of REM sleep and lasts about 100 minutes.

Subjects, methods, and results

The sleep of 16 healthy adults (10 women and 6 men) aged 52 to 67 years (mean 59 years) was recorded electrophysiologically on six consecutive nights every four weeks during a 16-week period. They were weighed in light clothing on the first and sixth nights. The first night of each six was for adaptation only. Recordings were from 10.15 pm to 7 am. The length of each successive sleep cycle in each of the 320 records was computed as the minutes elapsing between the beginning of one period of NREM sleep and the end of the following period of REM sleep. Cycles containing over one minute of wakefulness were excluded. The average length of the first, second, and third cycles in each subject’s 20 records was calculated and then the mean taken of the average of the first, second, and third cycles.

The mean of each subject’s eight weight measures was calculated and his or her standing height measured. The ideal body weight for each subject’s height4 was subtracted from their mean measured weight and the deviation expressed as a percentage of the ideal body weight. The percentage deviation from ideal body weight was significantly correlated with the mean NREM-REM cycle length ($r = -0.563$, $P < 0.03$, two-tailed) (figure), whereas mean body weight was not ($r = 0.104$, NS). The mean total minutes that subjects slept was also correlated with the percentage deviation from ideal body weight ($r = 0.536$, $P < 0.04$, two-tailed), and with the mean sleep cycle length ($r = 0.572$, $P < 0.03$, two-tailed).

Comment

These findings give further evidence for a connection between metabolism and sleep and show an association between a fundamental brain rhythm and the degree by which a person is under or overweight. The correlation with sleep duration confirms the common belief that

fat people sleep more than thin people, and it agrees with the reported shortening of sleep in obese patients when they reduce weight5 and the lengthening of sleep when anorectic patients regain weight.6

We thank Professor R W Gilliatt for permission to report this case and Dr W G Mair for performing the necropsy.

1 Mendowitz, M, Medicine (Baltimore), 1942, 21, 269.
5 Penfield, W, and Erickson, T, Epilepsy and Cerebral Localization. London, Baillière, Tindall, and Cox, 1941.

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Evaluation of digoxin capsules in outpatients

There are substantial individual differences in the dose of digoxin tablets required to maintain serum concentrations within the therapeutic range. A suitable dose cannot be predicted with confidence even by using nomograms which relate dose to endogenous creatinine clearance.7 This may be the result of variable absorption of digoxin from the tablets.8 Since absorption of digoxin from capsules (digoxin in a solution of polyethylene glycol encapsulated in soft gelatin) is virtually complete in normal subjects9 their use in patients might reduce the amount of trial and error in selecting a non-toxic but adequate dose. The following study tests this hypothesis.

Patients, methods, and results

Twenty outpatients (9 men and 11 women, aged 46 to 75 years, weighing 42 to 85 kg, and with a creatinine clearance of 37 to 120 ml/min) on maintenance therapy consented to participate. The patients were randomly allocated to receive for a period of four weeks either digoxin tablets (Lanoxin) (0.125, 0.1875, 0.25, 0.375, or 0.5 mg) or digoxin capsules (0.1, 0.15, 0.2, 0.3, or 0.4 mg daily) at 10 am. The tablet dose was equal to the total previously received in a day. The capsule dose was $80\%$ of the tablet dose. The dissolution rate of the tablets was greater than $90\%$ in one hour. At the end of the four-week period the patients crossed over to the alternative treatment. Patient compliance was encouraged by the use of calendar packs and “pill” counting.

During the fourth week on each formulation the following investigations...