malnourished patients but in none of the controls. Of the 10 patients with severe skin changes seven had evidence of viral persistence, which agrees with the findings of Scheifele and Forbes,[2] who found prolonged nasal giant cell excretion after measles in patients who had suffered severe skin change.

Despite the presence of giant cells, we could not culture measles virus from either nasal secretions or blood in any of our malnourished patients two to four weeks after the infection, although we had little difficulty in growing the virus from patients with acute measles. Our results suggest that these malnourished patients are unlikely to be infectious when they come to hospital.

The malnourished children showed severe impairment of cell-mediated immunity, which was probably the combined result of the immunosuppressive effects of their malnutrition and their persistent virus infection. Cell-mediated immunity to *Candida* was severely impaired, and six patients had oral candidiasis. This impaired immunity has also been found in malnourished children in Indonesia[12] and may result in candida infection in the gut.[13] The malnourished children also showed significantly less leucocyte inhibition to measles antigen than the controls. Although there is some doubt about whether this test is a specific measure of cell-mediated immunity,[14] we have found that non-immune cord blood lymphocytes show significantly less inhibition than immune lymphocytes, and we have also been able to reverse the inhibition to immune cells by using puromycin.[15] Thus we think that this difference between patients and controls probably indicates poorer cell-mediated immunity to measles in the malnourished children.

The malnourished children produced normal amounts of measles antibody, except for three whose lymphocytes were heavily infected with virus and all of whom died. The response to *S typhi* vaccine, which was mainly a secondary response, was not significantly different from that in the control group. Nevertheless, both groups showed a lower rise in titre than we have obtained in normal children with no recent history of measles.[16] The response to meningococcal group C polysaccharide, a primary response, was significantly depressed in the malnourished patients, suggesting that such children may have a poor response to coccal infections. This might make them susceptible to staphylococcal pneumonia, which is a very common cause of death after measles.[17]

Depression of the immune responses, such as we found in these children, is likely to increase the patients' susceptibility to secondary infections, and both viral and bacterial secondary infections were common. Such infections largely accounted for the high mortality among the malnourished children. Herpes virus was grown from the nasal secretions of three of the patients and this may have been disseminated in one child who died. We believe that persistence of measles virus plays an important part in the pathogenesis of malnutrition and debility after measles. The morbidity is mainly due to suppression of the immune response by the virus, which leads to secondary infections, rather than to the direct destructive action of the virus itself. Nevertheless, three of the patients in this study who died had heavy viraemia and low levels of antibody and clearly died from overwhelming measles infection.

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Requests for reprints should be sent to Dr J Dossetor.

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Unnecessary polypharmacy for epilepsy

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Summary

A retrospective survey of 50 adult epileptic outpatients who were taking two anticonvulsant drugs showed that seizure control had improved in the six months after the introduction of the second drug in only 36%. When blood concentrations of the two anticonvulsants were subsequently measured improvement in seizure control was found to be significantly related to the presence of optimum blood concentrations of at least one drug. Much unnecessary polypharmacy in the treatment of epilepsy could be avoided by ensuring an optimum blood concentration of one drug before considering the addition of a second.

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Introduction

Epileptics are commonly treated with more than one anticonvulsant drug. A survey in four European countries found that 11 720 patients, randomly selected from inpatient and outpatient populations, were receiving 3·2 drugs per patient, of which 84·3% were anticonvulsants.[1] We have been concerned at the extent of this polypharmacy for three reasons. Firstly,

there is growing evidence of the hazards of prolonged anticonvulsant treatment, which increase with the number of drugs taken.[2] Secondly, we are unaware of any definite evidence that two or more drugs are more effective than one in treating any particular type of epilepsy. Lastly, now that blood drug concentrations can be monitored we can use any individual anticonvulsant more effectively.[3-6]

In a prospective study 31 outpatients with grand mal or focal epilepsy, or both, were treated with phenytoin alone and their blood drug concentrations were monitored. Only three patients needed a second drug during a mean follow-up period of nearly 15 months, which suggested that many patients might be satisfactorily treated with one drug instead of the many that they usually receive.[6] We therefore reviewed the records of all adult epileptics taking two anticonvulsants who were attending the neurological outpatient department, King's College Hospital, to find out why they were treated with a second drug and to assess the impact of the second drug on seizure control.

Patients and methods

The case records of all the epileptics attending the neurological outpatient department of King's College Hospital in 1972-6 were surveyed. These years were chosen because blood level monitoring of anticonvulsants became available in the clinic in 1972, and, with the use of standardised questionnaires, the quality of documentation improved. Most of the patients surveyed had, however, already been attending the clinic for many years before 1972.

Out of 276 patients 82 were found to be taking two anticonvulsants at their last appointment during this period (172 were taking one, 17 were taking three, and five were taking four). Of these 82 patients 32 were excluded for the following reasons: in 15 documentation before 1972 was inadequate; seven were suffering from progressive cerebral disorders; five were taking anticonvulsants, the blood levels of which could not be monitored (sodium valproate, clonazepam); and in five the second anticonvulsant was ethosuximide, which had been prescribed to treat an additional petit mal component of their epilepsy. The remaining 50 patients (27 women and 23 men) were aged 15-80 years (mean 34·8 years). Seizures were classified as grand mal in 26 cases, focal minor (partial) in 16 (14 temporal lobe), and mixed grand mal and focal minor in eight (all temporal lobe). The drug combinations are summarised in table I.

TABLE I—*Combinations of drugs taken by the 50 patients*

Combination	No of patients	Combination	No of patients
Phenytoin and phenobarbitone	24	Primidone and carbamazepine	2
Phenytoin and primidone	19	Phenobarbitone and carbamazepine	1
Phenytoin and carbamazepine	3	Primidone and phenobarbitone	1

The frequency of seizures in the six months immediately before (baseline period) and after (first test period) the addition of the second drug was calculated. Patients whose seizure frequency had fallen from the baseline level by 50% or more in the test period were considered to have "improved." Anything less than a 50% reduction was categorised as "no improvement."

The relevance of subsequent blood anticonvulsant concentrations to seizure control was similarly assessed by comparing seizure frequency in the six months before the first blood level determination (second test period) with that in the baseline period. When there had been a change in drug dose within the second test period seizure frequency was calculated from the time of the last dose change. Patients were divided into three groups according to whether the blood levels of neither, one, or both anticonvulsants were in the optimum range. The optimum ranges used were: phenytoin 40-79 μmol/l (10-20 μg/ml); phenobarbitone 86-129 μmol/l (20-40 μg/ml), and carbamazepine 17-34 μmol/l (4-8 μg/ml). For primidone the blood concentration of derived phenobarbitone was used.

Serum phenytoin, phenobarbitone, and primidone concentrations were determined by the on-column methylation technique of Kupferberg[7] using a Hewlett-Packard series 5750 research gas chromatograph, 3% OV 17 columns, and 5-(*p*-methyl-phenyl)-5-phenylhydantoin as internal standard. Serum carbamazepine was measured by the gas chromatographic technique of Toseland *et al.*[8]

Results

The mean interval between the introduction of the first and second drugs was 2·4 years and that between the first and second test periods was 5·6 years. Forty-four patients had been given a second drug because of continuing seizures on a single drug, but six patients had been started on two drugs. We therefore assessed the effect of the addition of the second drug on seizure frequency in 44 patients. In 16 patients (five with grand mal and 11 with focal or mixed seizures) there was a 50% or more reduction in seizure frequency. But in the remaining 28 patients (18 with grand mal and 10 with focal or mixed seizures) there was no improvement.

The relationship of the first blood drug level determination to seizure control in the second test period is summarised in table II.

TABLE II—*Relation of first blood levels of anticonvulsant drugs to seizure control (second test period)*

Anticonvulsant concentrations in optimum range	Improved*	No improvement
Neither	4 (grand mal)	10 (6 grand mal; 4 focal or mixed)
Only one	15 (8 grand mal; 7 focal or mixed)	3 (1 grand mal; 2 focal or mixed)
Both	9 (4 grand mal; 5 focal or mixed)	1 (grand mal)

In eight cases blood drug concentrations were not measured.
*50% or more reduction in seizure frequency.

Improvement in seizure control was clearly related to an optimum blood concentration of one or both anticonvulsants. In 24 of the 28 cases in the improved group the blood concentration of at least one anticonvulsant was in the optimum range, whereas this was the case in only four of the 14 patients whose seizures were not improved ($P < 0.001$).

Discussion

As expected, most patients received the second anticonvulsant because of continuing seizures on one drug, presumably on the assumption that this would improve seizure control. Our findings cast some doubt on this assumption, as there was evidence of improvement (a reduction of half or more in the frequency of seizures) in only 16 out of 44 (36%) patients in the six months after the addition of the second drug, a period when maximum benefit might have been expected.[9] Whether this improvement was significantly better than that which might have been obtained with a placebo is at least open to question, and it still remains to be proved that two drugs are more effective than one in controlling the more severe forms of epilepsy. Surprisingly, treatment in six patients was started with two drugs, for which there seems to be no justification. In four patients this was done even when blood drug level monitoring was available.

The value of monitoring the concentration of anticonvulsants in the blood has already been established in our own and other prospective studies.[3-6] It has again been emphasised in our retrospective analysis of seizure control in relation to the first blood level determination, which showed that improved control was clearly related to the presence of optimum blood concentrations of at least one drug. Among the 16 patients who improved in the six months after the introduction of the second drug an optimum blood concentration of at least one drug was found in 12 of the 13 whose blood levels were subsequently determined. Improvement appears to be better related to blood concentrations of one drug than it is to the number of drugs administered.

We recognise that there are limits to the precision of a retrospective study such as this. For example, we cannot be

certain, and indeed it is unlikely, that the blood concentrations were constant throughout the six months before their determination. We were, however, careful to exclude patients whose documentation was inadequate, and the picture that emerged is consistent with the findings of our prospective study[6] and reinforces our view that many patients are unnecessarily treated with two (or more) drugs when one, guided by blood level monitoring, would do.

In conclusion, we suggest the following policy for treating new patients with any one type of seizure. The patient should be treated with one drug, which should be gradually increased in dose until seizures are controlled or, if seizures are continuing, until the blood drug concentration is at the higher end of the optimum range. Only when seizures continue despite an optimum blood concentration is it justifiable to consider adding a second drug (the possibility of an alternative drug should also be considered). In this way we believe that much unnecessary polypharmacy, with its attendant hazards, could be avoided. The fact that only 104 of our 276 patients were taking two or more drugs reflects the introduction of this policy in this clinic in the past three years.

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SIDE EFFECTS OF DRUGS

The relation of body weight to side effects associated with oral contraceptives

The concept of individual variation in response to a drug is valuable for clinicians who are trying to select the "right" oral contraceptive for each patient. Nevertheless, many formulas for taking account of patients' endogenous hormonal characteristics[1 2] are too complicated to be useful.[3] Body weight is usually taken into account in assessing the pharmacological effects of most drugs, and Hancock *et al* recently reported that underweight women were more likely to have amenorrhoea[4] after stopping oral contraceptives than other women. We therefore investigated the possible relation between body weight and the side effects experienced by women taking oral contraceptives.

Patients and methods

A double-blind crossover study of Ovral (ethinyloestradiol 0·05 mg and DL-norgestrel 0·5 mg), Norinyl 1/50 (mestranol 0·05 mg and norethindrone 1·0 mg), and Norlestrin (ethinyloestradiol 0·05 mg and norethinidrone acetate 1·0 mg) was performed in 1974–5.[5] Four hundred and eighty healthy women of reproductive age who had no menstrual abnormalities or contraindications to oral contraceptive use and who had used no steroidal contraceptives during their last three menstrual cycles were enrolled in the study. Each woman was given three cycles of one of the oral contraceptives, each cycle containing 21 hormonal and seven placebo tablets. The women were told to take one tablet each day and to return when their supply ran out. At the follow-up visit the patient received a further three months' supply. The oral contraceptives were randomly assigned to each woman at both the initial and follow-up visits. Thus some women continued to use the same brand of contraceptives while others received one of the other two brands.

The admission record collected information on weight, height, blood pressure, menstrual history, and selected demographic characteristics. Follow-up records seeking information on menstrual history, weight, and blood pressure, were completed after three and six cycles of oral contraceptive use.

Each woman was placed into one of the following groups on the basis of her weight at the time of enrolment into the study: (*a*) underweight—less than 90% of the national average[6] for her height and age; (*b*) normal weight—90 – 110% of the national average; (*c*) overweight—over 110% of national average. The 10% range for the underweight and overweight categories was based mainly on the consideration that at least 30 cases should be in the underweight and overweight categories for each contraceptive studied so that the incidence of side effects could be estimated reliably.

Information on side effects was collected by a nurse who telephoned each patient every two weeks. Each time the subject was asked whether she had experienced certain specified effects since the last contact. The incidence of side effects was defined as the percentage of women reporting that event, irrespective of its duration. The incidence rates of specific side effects varied with the different hormonal preparations,[5] but analysis by weight categories for each contraceptive suggested that the relation between the incidence of side effects and weight categories was similar for the three contraceptives. Data for all three contraceptives were therefore pooled. We considered each cycle separately since the incidence of specific side effects varies with the order of contraceptive cycle. The statistical significance of the incidence rates was tested by the one-tailed test.

Results

Almost all women in the study had been educated for 10 or more years. About 90% were aged under 25 years, Caucasian, and unmarried. Sixty per cent had used some form of contraception before entering the study. There were no significant differences in the distribution of these characteristics among the three weight categories. Although our weight categories were based on the women's expected weight according to height and age, we found that the same three categories would have resulted if the women had been grouped by their actual weight—that is, under 55 kg, 56–68 kg, and 69 kg or more.

Table I shows the percentage of women in each weight category reporting specific side effects during the first three cycles.

Breakthrough spotting or bleeding—There were no significant differences in the incidence of breakthrough spotting or bleeding between the three groups.

Menstrual cramps—Underweight women reported a higher incidence of menstrual cramps than normal or obese women. This relationship was suggested in the first cycle, but acquired statistical significance ($0·05 < P < 0·10$) during the second and third cycles. Normal and obese women showed no difference in the incidence of menstrual cramps.

Nausea—The incidence of nausea in overweight women was lower than that in normal or underweight women. The difference became highly significant ($P < 0·01$) in the second cycle.

Vomiting—Obese women reported a significantly lower incidence of vomiting ($P < 0·01$) than normal and underweight women. This difference existed only in cycles 1 and 2 and tended to disappear in cycle 3.

Headache—The incidence of headache during the first two cycles was significantly lower ($P < 0·05$) in normal women than in the other two groups. This pattern, with the lowest incidence in the normal weight category, was unique; the obese women usually had the lowest incidence of other side effects.

Depression—There was no association between depression and weight.

Breast discomfort—Overweight women reported a significantly lower ($P < 0·05$) incidence of breast discomfort than underweight or normal women who had similar incidences. The relationship persisted only during the first two cycles of contraceptive use.

Acne and sexual desire—No significant differences were observed.

Changes in menstrual bleeding—The women were also asked about any changes in their menstrual (withdrawal) bleeding during each cycle compared with their menses before using contraception (table I). During the first two