CARBAMAZEPINE AND CARBAMAZEPINE-10,11-EPOXIDE CONCENTRATIONS IN HUMAN BRAIN

P.L. MORSELLI*, A. BARUZZI, M. GERNA, L. BOSSI & M. PORTA¹

Istituto di Ricerche Farmacologiche Mario Negri Via Eritrea 62, Milan, Italy and

¹ Divisione de Neurochirurgia, Ospedale Maggiore Cà Granda, Milan, Italy

1 Carbamazepine (CBZ) brain and plasma concentrations were measured in twenty-one patients undergoing brain surgery for tumour removal. The drug was administered prophylactically at doses ranging from 6.9 to 14.8 mg/kg for 4–5 days before the intervention.

2 In seventeen cases where samples were collected 10–14 h after dosing, CBZ brain levels ranged from 2.2–14.5 µg/g. A significant linear relationship ($P < 0.01$) was observed between brain and plasma concentrations with a brain/plasma ratio of 1.1 ± 0.1 .

3 Carbamazepine-10,11-epoxide (CBZ-Epo), present in all samples, could be quantified in three brain specimens. Its brain concentrations ranged from 1.5–2.7 µg/g with a brain/plasma ratio of 1.1–1.2.

4 Parieto-occipital areas tended to show higher CBZ concentrations while lower values were found in temporal regions. Very low CBZ levels were found in two gliomas while in meningiomas CBZ levels were similar to those observed in normal tissue.

5 The data, showing a linear relationship between brain and plasma concentrations of both CBZ and its epoxide, give additional significance to the plasma level monitoring of antiepileptic drugs.

Introduction

Carbamazepine (CBZ) is a major antiepileptic agent and its clinical efficacy has been stressed by several authors (Cereghino, Brock, van Meter, Penry, Smith & White, 1974; Dalby, 1971; Monaco, Riccio, Benna, Covacich, Durelli, Fantini, Furlan, Gilli, Mutani, Troni, Gerna & Morselli, 1976; Rodin, Rim & Rennick, 1974; Troupin, Green & Levy, 1974). The pharmacokinetics and the metabolism of the drug have been extensively described in both experimental animals and man (Farghali-Hassan, Assael, Bossi, Gerna, Garattini, Gomeni & Morselli, 1976; Levy, Lockard, Green, Friel & Martis, 1975; Levy Pitlick, Troupin, Green & Neal, 1975; Morselli, 1975; Morselli & Frigerio, 1975; Morselli, Gerna & Garattini, 1971; Morselli, Bossi & Gerna, 1976).

A threshold brain level of 4.5–5 µg/g for protection toward maximal electroshock in the rat together with a brain/plasma ratio of 1–1.5 was observed after both single and repeated administrations (Farghali-Hassan *et al.*, 1976; Morselli, 1975; Morselli *et al.*, 1971).

The assessment of the ratios of brain to plasma concentrations for an anticonvulsant drug may be of relevance to therapy since a constant brain/plasma

ratio is one of the basic assumptions underlying the monitoring of anticonvulsant plasma levels in course of chronic treatment.

The existence of a constant brain/plasma ratio for phenytoin and phenobarbitone in man has recently been confirmed by Sherwin, Eisen & Sokolowski (1973), Vadja, Williams, Davidson, Falconer & Breckenridge (1974), and Houghton, Richens, Toseland, Davidson & Falconer (1975), while for CBZ only very preliminary data are available (Baruzzi, Porta, Gerna, Collice, Ferrara & Morselli, 1976; Morselli *et al.*, 1976).

In this report, extending our previous observations (Baruzzi *et al.*, 1976; Morselli *et al.*, 1976), we present data on brain and plasma levels of CBZ in neurosurgical patients who received the drug prophylactically before undergoing brain surgery.

Methods

Observations were carried out on twenty-one patients (32–69 years of age) of both sexes (twelve females and nine males) admitted for neurosurgery to the Neurosurgical Departments of the Ospedale Maggiore and the Istituto Neurologico C. Besta in Milan.

* Present address: Clinical Research Department, LERS-Synthelabo, 58, rue de la Glacière, 75013, Paris, France.

One patient (9) had an intracerebral haematoma, three patients (2, 11, 15) were affected by brain metastatic tumour and the remaining seventeen patients had primary intracranial tumours (two gliomas and twelve meningiomas). All patients gave fully informed consent to the observations.

CBZ treatment was administered prophylactically 4–5 days before the operation. Only in case 19 was CBZ treatment initiated only 18 h before surgery.

The doses of CBZ administered varied from 6.9–14.8 mg kg⁻¹ day⁻¹. Patient G.M. (8) was already on phenobarbitone treatment (1.5 mg/day) which was not discontinued. In nineteen cases the last dose of CBZ was administered 10–14 h before the operation, whereas in case number 19 (patient S.M.) the last dose was given 6 h before surgery and in case number 18 (patient V.M.) 17 h before.

In all patients blood samples were collected in heparinized test tubes after pre-anesthetic medication, immediately before surgery. Blood was centrifuged within 20 min and the plasma so obtained was kept at 4°C until analysis. Brain specimens were obtained about 1 h later than the plasma ones, they were frozen immediately at -60°C and kept frozen until analysis.

The 1 h delay between plasma and brain sampling was dictated by practical operative problems.

Considering that the patients should have been in steady state, and also on the basis of the CBZ half-life (~15 h) and of our previous observations (Morselli *et al.*, 1976), the relatively short time interval between plasma and brain sampling was not considered capable of affecting significantly the findings.

Normal tissue brain samples were obtained when the surgeon considered ablation of cortical tissue necessary for the intervention.

Mechanical ventilation maintained PaCO₂ between 25 and 30 mmHg and arterial PO₂ at about 200 mmHg.

In all cases standard anaesthetic medication and respiratory control were obtained by thiopental sodium (4 mg/kg), droperidol (2.5–5 mg *pro capite*), tubarine (20–30 mg *pro capite*), and fentanyl (0.1–0.5 mg *pro capite*).

Chemical analysis

Plasma samples were analyzed for CBZ and CBZ-Epoxy by a g.l.c. procedure as previously described by Morselli, Biandrate, Frigerio, Gerna & Tognoni (1973). The following procedure was used for brain samples: brain specimens were homogenized in 1.15% KCl (1:4 v/v); 3 ml of the homogenate were brought to pH 8 and extracted with 4 ml of toluene; 3 ml of the organic phase were then brought to dryness under nitrogen at 40–50°C. The drug residue was redissolved in 100 µl of acetone and 1 µl of this solution was injected onto the gas chromatograph; 4-(3,4,5-trimethoxy-benzoyl)-tetrahydro-1,4 oxazine (Italseber, Milan) was used as an internal marker.

Figure 1 Correlation between brain and plasma carbamazepine concentrations ($y = 0.55 + 0.99x$; $r = 0.82$; $P < 0.01$) ● = normal tissue; ■ = peritumoural tissue; ○ = glioma. Glioma values were not included in the analysis. Case number 20 (meningioma—brain/plasma ratio 1.1) and case number 19 (18 h of therapy—brain/plasma ratio ~0.3) are not reported in the graph and they were not included in the analysis.

The gas chromatographic conditions were identical to those described for plasma (Morselli *et al.*, 1973). The minimal detectable amount of CBZ in our conditions was 0.5 µg/ml of plasma and 1.2 µg/g of brain. The limits for the epoxide were 0.5 µg/ml in plasma and 1.5 µg/g in brain.

Results

Carbamazepine brain and plasma levels

A considerable interindividual variability in CBZ plasma levels (10–14 h after the last drug intake) was evident after 4–5 days of treatment at doses ranging from 6.9 to 14.8 mg/kg. Furthermore, there was no relationship at all between plasma levels and doses expressed either as total daily amount or as mg kg⁻¹ day⁻¹.

Individual CBZ plasma levels ranged from 2.2–13.7 µg/ml in twenty patients and they were of 1.4 µg/ml in patient S.M. (case number 19) who started CBZ treatment 18 h before surgery and had her plasma sample collected 6 h after the last dose. It may be worth noticing that ten out of twenty-one patients had CBZ plasma levels below 5 µg/ml (Table 1).

Brain CBZ concentrations ranged from 0.9–10.5 µg/g in fifteen specimens consisting of normal cortical tissue, and CBZ concentrations of 3.1–14.5 µg/g were found in three peritumoural tissue

specimens. The lowest brain CBZ concentration was found in patient number 19 who had just initiated treatment the day before.

Brain/plasma CBZ concentration ratios varied from 0.4–2.0 with most values ranging from 0.8–1.4 and a mean value of 1.1 ± 0.1 ($\pm$ s.e. mean). As shown in Figure 1, a linear positive relationship ($P < 0.01$) was found between brain and plasma concentrations. There was a trend to higher CBZ brain/plasma ratios in the parieto-occipital areas (1.50 ± 0.27) together with a trend for lower values in the temporal areas (0.75 ± 0.21), the difference between these two areas being significant ($P < 0.05$).

In four patients (numbers 7, 16, 20, 21) it was possible to analyse tumoural tissues and a different behaviour was observed between gliomas and meningiomas. For meningiomas, in case number 16, tumoural tissue CBZ concentration ($6.4 \mu\text{g/g}$) was very similar to that observed in the corresponding normal tissue ($5.4 \mu\text{g/g}$) and in case number 21 (where only the tumoural tissue could be analysed) the CBZ brain/plasma ratio was 1.1. On the contrary, in the case of gliomas CBZ was present at a concentration ($3.0 \mu\text{g/g}$) 40% lower than that observed in the normal tissue of the same patient (number 17), and was found only in traces ($\sim 0.6 \mu\text{g/g}$) in case number 20.

Table 1 Carbamazepine plasma and brain levels in neurosurgical patients following a repeated administration

Case	Age (years)	Dose (mg/kg)	Plasma levels ($\mu\text{g/ml}$)	Brain levels ($\mu\text{g/g}$)	Brain/plasma ratio	Interval from last dose (h)	Brain area	Tissue specimen
1 P.C.	50	6.9	8.7	9.6	1.1	13	Fr.Cx	Normal
2 E.C.	51	7.5	2.5	3.6	1.4	14	Pt.Oc.Cx	Normal
3 A.F.	68	8.1	4.0	4.4	1.1	14	Fr.Cx	Normal
4 R.B.	61	12.3	8.0	6.3	0.8	14	Fr.Cx	Normal
5 G.B.	41	8.7	8.7	9.7	1.1	13	Fr.Cx	Normal
6 C.L.	53	14.2	2.2	2.2	1.0	14	Tp.Cx	Normal
7 M.B.	53	11.7	7.3	7.2	0.9	14	Fr.Cx	Normal
8 G.M.	63	9.2	4.4	4.1	0.9	13	Fr.Cx	Normal
9 A.C.	59	9.7	6.8	8.6	1.2	14	Tp.Cx	Normal
10 A.A.	69	10.0	6.0	6.1	1.0	13	Fr.Cx	Normal
11 P.R.	54	11.7	3.9	3.1	0.8	14	Fr.Cx	Peritumoural
12 F.S.	62	10.2	5.7	7.7	1.3	14	Pt.Cx	Peritumoural
13 M.S.	54	14.8	13.7	14.5	1.1	14	Oc.Cx	Peritumoural
14 F.L.	52	8.8	5.1	10.5	2.0	10	Pt.Oc.Cx	Normal
15 M.S.	69	8.5	4.5	9.0	2.0	13	Fr.Cx	Normal
16 C.A.	44	11.0	8.0	5.4	0.7	10	Fr.Cx	Normal
17 A.V.	49	12.1	3.4	1.9	~ 0.5	14	Tp.Cx	Normal
18 V.M.	32	11.0	2.2	0.9	0.4	17	Fr.Cx	Normal
19 S.M.	54	8.8	1.4	< 0.5	~ 0.3	6	Tp.Cx	Normal

Fr.Cx=Frontal cortex; Pt.Oc.Cx=Parieto-occipital cortex; Tp.Cx=Temporal cortex; Oc.Cx=Occipital cortex. For case numbers 20 and 21, where only tumoural specimens were available, plasma concentrations were 3.6 and $5.6 \mu\text{g/ml}$. For tumoural tissue concentrations see text.

Table 2 Carbamazepine-10,11-epoxide concentrations in human brain following repeated CBZ administration

Case	Plasma epoxide ($\mu\text{g/ml}$)	Brain epoxide ($\mu\text{g/g}$)	Brain/plasma ratio	Epo/CBZ plasma	Epo/CBZ brain
3 A.F.	2.18	2.72	1.24	0.50	0.61
7 M.B.	1.67	2.05	1.22	0.22	0.28
21 B.O.	1.31	1.52	1.16	0.23	0.24

All three specimens were frontal cortex. Case numbers 3 and 7 were normal tissues; case number 21 was tumoural tissue (meningioma).

Carbamazepine-10,11-epoxide brain and plasma levels

Carbamazepine-10,11-epoxide was found present in all brain and plasma samples analysed with the exception of the brain specimens of case numbers 19 and 20. However, for technical reasons, its precise quantitation in brain was possible only in three cases (numbers 3, 7, 21). These data are reported in Table 2. It can be observed that the compound was present at concentrations of the same order as the plasma ones, with brain/plasma concentration ratios ranging from 1.6–1.24. Furthermore, it might be interesting to notice that the ratios of the epoxide to CBZ in the brain specimens were very similar to those observed for plasma.

Discussion

It is generally assumed, mainly from data in animals (Celesia, Booker & Sato, 1974; Firemark, Barlow & Roth, 1963; Kutt, Louis & McDowell, 1968; Morselli *et al.*, 1971; Rizzo, Morselli, & Garattini, 1972) that plasma levels of anticonvulsant drugs are related to brain concentrations by a constant ratio.

Data from humans are extremely scarce and only recently Sherwin *et al.* (1973), Vajda *et al.* (1974), and Houghton *et al.* (1975) could confirm that for phenobarbitone and phenytoin the brain/plasma ratio in man is of the same order as that observed in experimental animals. The data presented in this report indicate that also for CBZ the ratio between brain and plasma concentrations is relatively constant in man and confirm previous observations in experimental animals (Farghali-Hassan *et al.*, 1976; Morselli, 1975; Morselli *et al.*, 1971).

CBZ absorption may be very erratic (Morselli, Monaco, Gerna, Recchia, Riccio, 1975) and the difference in the absorption rate could partially explain the considerable degree of variability in plasma and tissue levels among the various patients. A delayed and impaired absorption could very well sustain the lowest values.

The significant relationship between brain and plasma concentrations ($P < 0.01$) indicates that plasma levels monitoring may be a useful index of brain concentration for CBZ also. Although brain levels do not necessarily provide an indication of drug levels at the receptor sites (data on this topic are missing for all anticonvulsants), according to our experience in both experimental animals (Farghali-Hassan *et al.*, 1976; Morselli *et al.*, 1971) and epileptic patients (Morselli, 1975; Morselli *et al.*, 1976), the minimal effective concentration of CBZ in brain and plasma is of about 4.5–5 µg/ml, while for plasma levels over 12 µg/ml disturbing side effects may be very frequent.

A prophylactic treatment starting 96–120 h before

surgery, does not seem to allow the building up of effective brain levels in about 50% of patients. This point stresses the need for monitoring plasma levels during the pre-operative treatment.

Carbamazepine-10,11-epoxide, the main active metabolite of CBZ (Morselli, 1975), was measured for the first time in human brain. These data are in good agreement with the recent findings of Johannessen Gerna, Bakke, Strandjord & Morselli (1976) who could measure the epoxide in the CSF of epileptic patients under chronic treatment with CBZ. Furthermore, the presence of CBZ-Epox in the human brain at concentrations similar to the plasma ones, gives additional support to the suggestion that this important metabolite of CBZ should be constantly measured when monitoring CBZ plasma levels (Johannessen *et al.*, 1976; Morselli, 1975). It has in fact been shown that the compound is an active agent against experimental seizures with a potency similar to that of CBZ (Frigerio & Morselli, 1975).

We have no explanation for the low CBZ concentrations in the two gliomas. The data could be related to the abnormal vascularity of the tumour itself: their bearing for anticonvulsant therapy does not seem significant since the higher drug concentration in the peritumoural tissues should be capable of interfering with the spreading of the electrical discharge. The observation, however, if supported by similar findings in a larger number of cases, could be of some relevance for the chemotherapeutic approach of treating brain tumours.

As regards the possibility of a different CBZ distribution in various brain regions, a trend toward higher values in the parieto-occipital areas was observed even though the small number of cases does not allow definite conclusions. Such findings are in good agreement with the reports on phenytoin by Sherwin *et al.* (1973), who described lower values in temporal areas and higher ones in parieto-occipital areas.

In neurosurgical patients, in our experience, CBZ is better tolerated than phenytoin and phenobarbitone, and its use appears preferable in patients undergoing deep anaesthesia. In fact, at variance with phenytoin and phenobarbitone, the body distribution of CBZ (because of its different physico-chemical properties), is less affected by blood and tissue pH changes. Furthermore, at the levels usually achieved with therapeutic doses, it does not depress cardiac and respiratory centres.

The correct prophylactic treatment of neurosurgical patients is a problem of primary importance. De Vet & Ponssen (1962) observed that about 33.9% of the patients submitted to brain surgery for tumour removal developed seizures. The same incidence of seizures has been reported by Peserico, Nori & Ravenna (1965). Despite the fact that the importance of a correct prophylactic treatment in patients undergoing brain surgery has been stressed several

times (Gaches & Suprino, 1970; Northcroft & Wike, 1957; Terzian, 1953, 1954), quantitative data on this subject are very scanty indeed as recently underlined by Rapport & Penry (1973).

On the whole, our data stress the need for a careful anticonvulsant drug plasma levels monitoring in course of prophylactic treatment of neurosurgical

patients, and suggest that CBZ should be a useful alternative to phenobarbitone.

The authors wish to express their appreciation to Professor G. Morello (Istituto Neurologico C. Besta), and Professor A. Beduschi (Ospedale Maggiore Cà Granda) for their clinical and neurosurgical cooperation to the study, and to Dr R. Gomeni for the statistical analysis of the data.

References

- BARUZZI, A., PORTA, M., GERNA, M., COLLICE, M., FERRARA, M. & MORSELLI, P.L. (1976). Brain and plasma concentrations of carbamazepine in neurosurgical patients. *Acta Neurochirurgica* (abstract) (in press).
- CELESIA, G.G., BOOKER, H.E. & SATO, S.E. (1974). Brain and serum concentrations of diazepam in experimental epilepsy. *Epilepsia*, **15**, 417–425.
- CEREGHINO, J.J., BROCK, J.T., VAN METER, J.C., PENRY, J.K., SMITH, L.D. & WHITE, B.B. (1974). Carbamazepine for epilepsy. *Neurology*, **24**, 401–410.
- DALBY, M.A. (1971). Antiepileptic and psychotropic effect of carbamazepine (Tegretol) of psychomotor epilepsy. *Epilepsia*, **12**, 325–334.
- DE VET, A.C. & PONSSEN, H. (1962). Meningiomes intracranies et épilepsie. *Neurochirurgie*, **8**, 363–369.
- FARGHALI-HASSAN, ASSAEL, B.M., BOSSI, L., GERNA, M., GARATTINI, S., GOMENI, R. & MORSELLI, P.L. (1976). Carbamazepine pharmacokinetics in young, adult and pregnant rats. Relation to pharmacological effects. *Arch. Pharmacodyn.*, **219**, 197–211.
- FIREMARK, H., BARLOW, C.F. & ROTH, L.J. (1963). The entry accumulation and binding of diphenylhydantoin-2-¹⁴C in brain. Studies on adult, immature and hypercapnic cats. *Int. J. Neuropharmacol.*, **2**, 25–38.
- FRIGERIO, A. & MORSELLI, P.L. (1975). Carbamazepine: biotransformation. In *Advances in Neurology*, vol. 11, ed. Penry, J.K. & Daly, D.D., pp. 295–308. New York: Raven Press.
- GACHES, J. & SUPRINO, V. (1970). Etude de séquelles épileptiques dans 28 cas de méningiomes opérés et suivis plus de 10 ans. *Neurochir.*, **6**, 489–512.
- HOUGHTON, G.W., RICHENS, A., TOSELAND, P.A., DAVIDSON, S. & FALCONER, M. (1975). Brain concentrations of phenytoin, phenobarbitone and primidone in epileptic patients. *Eur. J. clin. Pharmacol.*, **9**, 73–78.
- JOHANNESSEN, S., GERNA, M., BAKKE, J., STRANDJORD, R.E. & MORSELLI, P.L. (1976). CSF concentrations and serum protein binding of carbamazepine and carbamazepine, 10-11, epoxide in epileptic patients. *Br. J. clin. Pharmacol.*, **3**, 575–582.
- KUTT, H., LOUIS, S. & McDOWELL, F. (1968). Intravenous diphenylhydantoin in experimental seizures—correlation of dose, blood and tissue level in cats. *Archives Neurology (CHIC)*, **18**, 465–471.
- LEVY, R.H., LOCKARD, J.S., GREEN, J.R., FRIEL, P. & MARTIS, L. (1975). Pharmacokinetics of carbamazepine in monkeys following intravenous and oral administration. *J. pharm. Sci.*, **64**, 302–307.
- LEVY, R.H., PITLICK, W.H., TROUPIN, A.S., GREEN, J.R. & NEAL, J.M. (1975). Pharmacokinetics of carbamazepine in normal man. *Clin. Pharmac. Ther.*, **17**, 657–668.
- MONACO, A., RICCIO, A., BENNA, P., COVACICH, A., DURELLI, L., FANTINI, M., FURLAN, P.M., GILLI, M., MUTANI, R., TRONI, W., GERNA, M. & MORSELLI, P.L. (1976). Further observations on carbamazepine plasma levels in epileptic patients. *Neurology*, **26**, 936–943.
- MORSELLI, P.L. (1975). Carbamazepine: absorption, distribution and excretion. In *Advances in Neurology*. Vol. 11, ed. Penry, J.K. & Daly, D.D., pp. 279–292. New York: Raven Press.
- MORSELLI, P.L., BIANDRATE, P., FRIGERIO, A., GERNA, M. & TOGNONI, G. (1973). Gas chromatographic determination of carbamazepine, 10-11, epoxide in human body fluids. In *Methods of Analysis of Anti-epileptic Drugs, Excerpta Medica*, ed. Meijer, J.W.A., pp. 169–175. Amsterdam.
- MORSELLI, P.L., BOSSI, L. & GERNA, M. (1976). Pharmacokinetics studies with carbamazepine in epileptic patients. In *Epileptic Seizures-Behavior-Pain*. ed. Birkmajer, W., pp. 141–150. Berne/Stuttgart/Wien: Huber, H., publ.
- MORSELLI, P.L. & FRIGERIO, A. (1975). Metabolism and pharmacokinetics of carbamazepine. *Drug Metabolism Reviews*, **4**, 97–113.
- MORSELLI, P.L., GERNA, M. & GARATTINI, S. (1971). Carbamazepine plasma and tissue levels in the rat. *Biochem. Pharmacol.*, **20**, 2043–2047.
- MORSELLI, P.L., MONACO, F., GERNA, M., RECCHIA, M., RICCIO, A. (1975). Bioavailability of two carbamazepine preparations during chronic administration to epileptic patients. *Epilepsia*, **16**, 759–764.
- NORTHCROFT, G.B. & WIKE, B.D. (1957). Seizures following surgical treatment on intracranial abscess, a clinical and electroencephalographic study. *J. Neurosurg.*, **14**, 249–263.
- PESERICO, L., NORI, A. & RAVENNA, C. (1965). L'epilessia post-operatoria nei meningiomi endocranici. *Min. Neurochirurgica*, **13**, 196–211.
- RAPPORT, R.L. & PENRY, J.K. (1973). A survey attitude towards the pharmacological prophylaxis of post-traumatic epilepsy. *J. Neurosurg.*, **38**, 159–166.
- RIZZO, M., MORSELLI, P.L. & GARATTINI, S. (1972). Further observations on the interactions between phenobarbital and diphenylhydantoin during chronic treatment in the rat. *Biochem. Pharmacol.*, **21**, 449–454.
- RODIN, E.A., RIM, C.S. & RENNICK, P.M. (1974). Effect of carbamazepine on patients with psychomotor epilepsy: results of a double blind study. *Epilepsia*, **15**, 547–561.
- SHERWIN, A.L., EISEN, A.A. & SOKOLOWSKI, C.D. (1973). Anticonvulsant drugs in human epileptogenic brain. *Arch. Neurology*, **29**, 73–77.
- TERZIAN, H. (1953–54). Le epilepsie dopo intervento neurochirurgico. *Rass. Neurol. Veget.*, **10**, 646–651.

TROUPIN, A.S., GREEN, J.R. & LEVY, R.H. (1974). Carbamazepine as an anticonvulsant: a pilot study. *Neurology*, **24**, 863-869.

VADJA, F., WILLIAMS, F.M., DAVIDSON, S., FALCONER, M.A. & BRECKENRIDGE, A. (1974). Human brain,

cerebrospinal fluid and plasma concentrations of diphenylhydantoin and phenobarbital. *Clin. Pharmac. Ther.*, **15**, 597-603.

(Received November 5, 1976)