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An audit of therapeutic drug monitoring of anticonvulsants

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SUMMARY

An audit of therapeutic drug monitoring (TDM) of anticonvulsants was performed to assess both its use and misuse in the management of patients with epilepsy. Over a four week period all samples received for phenytoin, carbamazepine, sodium valproate and phenobarbitone assays were included in the audit. The aims were to establish the source of the specimens, the reasons for the requests and to ascertain what action, if any, would be taken when the result of the assay was provided. A total of 163 separate assays were performed over the four week period (43 phenytoin, 74 carbamazepine, 41 valproate, 5 phenobarbitone). Only 18.7% of all requests originated from the adult neurology department. The vast majority of tests had been ordered by junior medical staff (only 10% by consultants) and approximately 50% were 'routine' with no satisfactory clinical reason for the request offered. There was a tendency to manipulate prescribed doses on the basis of drug levels alone without taking the clinical picture into consideration. These results demonstrate a general ignorance, especially amongst junior medical staff, of the value of TDM of anticonvulsants, and reinforce the need for both an educative and interpretive service to be provided by the Chemical Pathology Department.

INTRODUCTION

Therapeutic drug monitoring (TDM) may be defined as the use of drug measurements in body fluids as an aid to the management of patients receiving drug therapy for the cure, alleviation or prevention of disease.[1] Several clinical studies have demonstrated benefit in utilising TDM to individualise dosing regimens in patients on anticonvulsant drugs where pharmacological response is not so easily established by clinical means or laboratory markers.[2-4] Although TDM assists in the optimisation of anticonvulsant therapy, clinical and other criteria are important and TDM should never be used as the sole basis for making dosage adjustments.[5] However there are few prospective studies showing any substantial long term benefit to patients from TDM of anticonvulsant, and some of the anticonvulsant drugs do not fulfil the criteria that are necessary for valid TDM. These criteria include:

a). a narrow therapeutic index.

b). a close concentration-effect relationship.

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c). absence of clinical markers of effect. (If the desired effect can be quantified by simple clinical measurements TDM are of little benefit.)

d). poor correlation between dose and plasma concentration or effect.

There is an impression of a general ignorance, especially among junior medical staff, with regard to the value and use of TDM of anticonvulsants and this has led to a large increase in demand for these tests and subsequent laboratory workload over the past 10-15 years. Indeed some reviews of TDM, in general, point to misuse and misapplication and a failure to apply the criteria for effective TDM.[6] In today's stringent financial climate there is also the issue of costs versus benefits to patients. Some reviews suggest that an education system, with help in interpretation of results to the prescribing doctor should be a high priority in centres performing these assays.[7] The concept of normal therapeutic ranges is controversial as frequently patients with epilepsy will have satisfactory control of seizures at levels below the normally accepted therapeutic range [8] while others require concentrations in excess of the normal therapeutic range without displaying toxic effects.[9,10] In view of these factors there is the potential for misuse and misinterpretation of TDM of anticonvulsants. The monitoring of patients whose seizures are well controlled and who are free of toxic side effects is also questionable.

It is because of these factors that this audit was performed to assess TDM of anticonvulsants in a teaching hospital, to establish why the test was requested, to assess the impact of the result on patient management and whether to attempt to provide an educative and interpretive service.

PATIENTS AND METHODS

Over a four week period in June 1993, all samples received by the biochemistry laboratory of the Royal Group of Hospitals, Belfast, for TDM of phenytoin, carbamazepine, sodium valproate and phenobarbitone were audited. The Royal Group of Hospitals is a major teaching hospital, with amongst other disciplines, an Accident and Emergency department, a respiratory intensive care unit, a paediatric department and the regional neurology and neurosurgery service. The source of the samples was identified and the drug assays were all performed using the established FPIA (fluorescence polarisation immunoassay) method (Abbott Diagnostics, Maidenhead, Berkshire, UK). Anticonvulsant assays were performed in batches on a twice weekly basis and the need for emergency assays at other times (including those outside normal laboratory working hours) was assessed by the Chemical Pathology registrar.

When the assay results were available the ward, out-patient department or general practitioner was phoned by the registrar (PCS) and the doctor who had ordered the test was contacted (e.g. if a senior house officer had ordered a test on a consultant's instructions, the consultant was contacted). The reason for the request was ascertained and the result of the assay given with the 'normal' therapeutic range, and the doctor was asked in view of this, as to what action, if any, would be taken in the prescribed dose for the patient. Subsequently he was given information on the interpretation of the result. All requests were allocated to one of 7 groups on the basis of the stated reason for the request, thus:

1. No specific indication ('routine'). The patient's epilepsy was well controlled and there was no clinical suspicion of toxicity.

2. A recent increase in the number of seizures, before which control had been reasonable, or continuing seizures (? compliance problem or too low a prescribed dose).

3. Recent change in dose of the medication, or had recently been commenced on the medication.
4. Possible symptoms and signs of toxicity and a drug level requested to verify this.
5. Status epilepticus.
6. Patient on potentially interacting drugs.
7. Overdose of anticonvulsant.

RESULTS

Over the four week period a total of 139 samples were received. Four of these were emergency samples which were performed outside of normal laboratory hours by the on-call technician (two overdoses in adults, one child with probable toxicity and another with status epilepticus in the children's intensive care unit). One hundred and fifteen (115) patients were on monotherapy to control their epilepsy while the other 24 patients were on two medications requiring the analysis of two separate anticonvulsant drugs, making a grand total of 163 separate assays (43 phenytoin, 74 carbamazepine, 41 valproate and 5 phenobarbitone). The sources of the requests are given in Table I and the reasons for the requests in Table II. Ten percent of the total hospital requests had been ordered by consultants, 22% by senior registrars/registrars and 68% by senior house officers. 11.5% of patient requests originated from general practice.

Phenytoin (26.4% of all requests)

In 20 routine assays (47% of phenytoin requests) in patients who were clinically well with no signs of toxicity, 18 out of 20 (90%) lay in the normal therapeutic range (10-20 mg/l), one was lower (6.4 mg/l), but no change in dosage was made, and one was higher (28.3 mg/l):

TABLE I

Sources of requests for TDM of anticonvulsants

Source	*Number of Patients*
Medical Wards	21 (15%)
Surgical Wards	5 (3.6%)
Medical Outpatients	18 (12.9%)
Neurology Outpatients	15 (10.8%)
Neurology Inpatients	11 (7.9%)
Intensive Care Unit	5 (3.6%)
Childrens Hospital Inpatients	28 (20.1%)
Childrens Hospital Outpatients	12 (8.6%)
Accident and Emergency	4 (2.9%)
Other Hospitals	4 (2.9%)
General Practice	16 (11.5%)

in this case a dose reduction was made even though the patient had no toxic symptoms. In the seven assays performed due to recent increased episodes of seizures, six out of seven displayed levels lower than the therapeutic range in keeping with either a compliance problem or too low a prescribed dose (all six either confronted the patient with regard to compliance or increased the prescribed dose), the other result was in the therapeutic range. In six cases of suspected toxicity, four were in the toxic range and the other two were in the upper normal range: in all cases a dose reduction was made. Five out of the six assays for status epilepticus were in a single patient receiving intravenous phenytoin.

TABLE II

Reasons for requests for TDM of the different anticonvulsants

Reason for request	*Phenytoin*	*Carbamazepine*	*Valproate*	*Phenobarbitone*
1. Routine level	20 (46.5%)	36 (48.6%)	26 (63.4%)	2 (40%)
2. Continuing seizures	7 (16.3%)	19 (25.7%)	12 (29.3%)	3 (60%)
3. Recent dose change	2 (4.7%)	8 (10.8%)	1 (2.4%)	0
4. Possible toxicity	6 (14.0%)	9 (12.2%)	1 (2.4%)	0
5. Status Epilepticus	6 (14.0%)	0	0	0
6. Interacting Drugs	0	1 (1.4%)	0	0
7. Overdose	2 (4.7%)	1 (1.4%)	1 (2.4%)	0

Carbamazepine (45.3% of all requests)

In 36 routine assays (49% of carbamazepine requests), 29 were in the normal therapeutic range (8-12 mg/l), four were lower with no increase in dose being prescribed and three were above the normal range (two patients had their dose reduced even though they were well with no toxic symptoms). In 19 patients with recent seizures, 14 were below the therapeutic range and the dose was either increased or the patient challenged regarding compliance. In the nine suspected toxicities, seven out of nine were in the 'toxic' range with the other two at the upper limit of the normal range: all doses were reduced.

Sodium Valproate (25.2% of all requests)

Out of 26 routine assays (63% of valproate requests), 13 were in the normal range, ten were below the therapeutic range (eight of these patients were either challenged with regard to compliance or had their prescribed doses increased) and three patients had valproate concentrations higher than the therapeutic range (all had their prescribed dose reduced). In the 12 patients with recent increase in seizures, six had levels lower than the normal therapeutic range and the other six lay in the therapeutic range; the six with the low levels had their doses increased. The one patient with suspected toxicity had a level in the normal range and the dose was reduced. The one overdose patient had a level of 610 mg/l but remained perfectly well with apparently no side effects.

Phenobarbitone (3.1% of requests)

Two routine (40%) checks had normal therapeutic levels, and of the three patients with recent increasing seizures, two had levels below the therapeutic range and doses were increased: one had a normal therapeutic level but nonetheless the prescribed dose was also increased.

DISCUSSION

This audit illustrates that there is misunderstanding with regard to the concept and uses of TDM of anticonvulsant drugs. Of particular interest is the fact that the vast majority of tests were ordered by junior medical staff and a comparatively small number (18.7% of requests) came from the adult neurology in-patient and out-patient departments, despite the fact that this department manages most patients with epilepsy. This most probably reflects their greater understanding of the usefulness of TDM in different circumstances. Also of interest is the fact that for approximately half of requests there was no specific indication for drug level measurement. Only one of this type of request came from the neurology department. It appears that there is little potential benefit to the patient in this category as the majority of levels lie within the normal therapeutic range. Of more concern is that in patients with well controlled epilepsy, without toxic side effects, but with drug levels above the therapeutic range, there was a tendency to 'treat' the drug level and reduce the dose, despite the fact that some of these patients may require higher plasma concentrations to control their seizures. From this audit we can also see that most of those with either recent increasing incidence of seizures or with suspected toxicity displayed the appropriate low or high levels respectively and that clinical judgement was accurate. The notable exception to all of the above is sodium valproate. This drug displays a wide circadian variation with plasma concentrations varying by as much as 100% across the dosage interval. The normal therapeutic or target range is difficult to define, plasma concentrations are no better a guide to clinical response than is dose, and toxic effects show no clear relationship with level. These facts are borne out by our results and it is suggested that routine monitoring should not be practised and is, in fact, potentially misleading.[11, 12]

Monitoring of carbamazepine can be of use in some circumstances. The major problem with its measurement relates to its metabolism in the liver to carbamazepine–10, 11–epoxide, which is active but is not measured in most routine assays, including our own. However, the active metabolite can be measured using HPLC (high performance liquid chromatography), but this is not routinely available in most biochemistry laboratories and is expensive and time consuming to perform. Monitoring of carbamazepine is also complicated by individual pharmacodynamic variability; it induces its own metabolism and its metabolism can be altered by other anticonvulsants. The dosage of carbamazepine is a poor guide to plasma concentration and TDM is useful when seizure control is difficult.[13, 14]

Of all the anticonvulsants phenytoin appears to be the most useful to monitor.[15] It displays dose dependent pharmacokinetics and the hepatic system which metabolises it can become saturated, meaning that there is a non-linear relationship between dose and plasma concentration with the saturation levels varying between individuals. The normal therapeutic range has been designated 10-20 mg/l but some patients are controlled both at lower and higher levels and the prescribed dose of phenytoin should not be reduced on the basis of a high level if the patient is free from side effects.

With phenobarbitone, tolerance can develop on longer term therapy and there is a poor correlation between plasma concentration and adverse effects, and very low levels can have significant antiepileptic effects. There is a potential interaction with valproate which can lead to high phenobarbitone levels but in general TDM is not of much use except in children.

The results of this audit demonstrate an apparent lack of knowledge with regard to the value and use of TDM of anticonvulsants and a tendency to perform levels as a matter of routine. There is also a tendency to manipulate drug doses on the results of plasma levels alone,

aiming to establish the patient in the centre of the normal therapeutic range without taking the whole clinical picture into consideration. It is widely recognised that phenytoin is the most helpful drug to monitor because of its saturation kinetics, and that monitoring sodium valproate offers little reliable information and in fact can be misleading. The need to monitor patients whose seizures are well controlled is debatable and therapeutic decisions should never be based solely on drug concentrations. TDM can be useful in the assessment of non-compliance. For instance, repeatedly zero plasma concentrations in a patient who is 'well controlled' probably indicates misdiagnosis or that therapy is no longer required. The 'normal' therapeutic range should be used for guidance only with the knowledge that some patients may be well controlled at lower or higher levels and similarly patients can display toxicity in the normal therapeutic range. Patients on two or more medications merit more regular monitoring as there is potential for drug interactions and it can be difficult to tell which drug is causing possible toxic side effects or is not being prescribed in an appropriate dose. Education provided by the laboratory into the interpretation of results is essential and it is envisaged that guidelines will be drawn up to help medical staff. Cost effectiveness is of major importance in today's climate and the question should be asked "Is knowing a drug level going to help me in the management of this patient at this particular time?"

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