Benzodiazepines sensitivity testing

A pragmatic clinical approach to identify potentially useful GABAergic antiepileptic medications

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ABSTRACT

الأهداف: تحديد إمكانية الاستفادة من اختبار حساسية مجموعة أدوية التشنجات التابعة للبنزوديازبين (BZD) لانتقاء عقار فعال للتحكم بالتشنجات.

الطريقة: أجري اختبار على 76 حاله من الذين لديهم صرع في سن الطفولة غير متحكم به، اللذين راجعوا المستشفى الملكي بادنبره لأمراض الأطفال – ادنبرة، في الفترة مابين فبراير 2005م وحتى فبراير 2006م. كانت أسباب وأنواع التشنجات العصبية متباينة جداً، وكذلك التخطيط الفسيولوجي للدماغ (EEG). تم تصنيف التخطيط الدماغي (EEG) لهؤلاء الأطفال بعد الفحص إلى: تغير كامل، تغير متوسط، ولا يوجد تغير، وتغير انعكاسي. وصُنِفَ التحسن الإكلينيكي إلى: تحسن كامل، تحسن جزئي، ولا يوجد تحسن.

النتائج: نسبة كبيرة من التحكم الكامل بالتشنجات كانت نتيجة الفحص لديها تغير كامل بالتخطيط الفسيولوجي للدماغ، وتقل هذه النسبة تبعاً لوجود شحنات كهربائية، وكذلك مع اضمحلال وتقلص الموجات التخطيطية من نوع بيتا، والتي تشير إلى عدم حيوية قشرة الدماغ. إن المنطقة التخطيطية من الدماغ المتصاحبة مع وجود موجات كهربائية، وتحتوي على عدد قليل من الموجات التخطيطية من نوع بيتا، والتي سريرياً تكون متصاحبة مع آفة دماغية، قد تشير إلى قلة في مستقبلات القابا (GABA).

خاتمة: اختبار الاستجابة لمجموعة أدوية التشنجات التابعة للمجموعة البنزوديازبين (BZD)، قد يكون لها تأثير علي اختيار الأدوية المكافحة للتشنجات لعلاج الصرع.

Objective: To determine how benzodiazepine (BZD) sensitivity testing might be utilized to choose potentially useful antiepileptic drugs.

Methods: A retrospective audit of BZD sensitivity testing was carried out on 76 difficult pediatric epileptic cases that attended the Pediatric Neurology services at The Royal Hospital for Sick Children Edinburgh, Scotland from February 2005 to February 2006. The causes and types of epilepsy varied widely, as well as the encephalographic (EEG) findings. The EEG changes post-test are categorized according to the response to BZDs into "complete," "intermediate," "paradoxical" and "absent response." Similarly, the clinical outcomes after changing their antiepileptic medications have different ranges of clinical improvement from "definitive," "partial" and "no improvement."

Results: The largest percentages of definitive improvement are seen in those with complete response. The percentage with clinical improvement tends to decrease a) with increasing numbers and amplitudes of spikes that are resistant to the action of BZD, and b) when there is a paucity of, and different distribution of fast rhythms, indicating non-viability of cortical tissues. High spike density regions in the EEG pre-test that correlate with a specific pathology, and are found post-test to be devoid of fast rhythms, may indicate focally damaged gamma-aminobutyric acid receptor areas.

Conclusions: The BZD sensitivity testing may influence the choice of anticonvulsants in the management of epilepsy.

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The electroencephalogram (EEG) is routinely used as an investigation for paroxysmal disorders including the electrical cerebral dysrhythmias - the epilepsies. Its use in monitoring treatment has recently increased with the recognition that certain drugs, particularly antiepileptic medications (AEDs), leave a characteristic signature on the EEG. The benzodiazepine (BZD) group of AED's are quickly absorbed and concentrated in the cerebral cortex, and leave a definitive signature. The main inhibitory neurotransmitter is gamma amino-butyric acid (GABA), and drugs which enhance the effect of GABA at the chloride ionophore lead to an increase in intracellular anions.[1] The cell is therefore, more difficult to depolarize and is thus neuroinhibitory. The mainstay of treatment of the genetic and malignant epilepsies of childhood is GABA medications. Because of BZDs character of rapid absorption and quick brain penetration, they serve as a useful model for the study of electrical signatures and are clinically useful in the emergency treatment of status epilepticus or as a rescue medication for non-self terminating seizures, and also as a test for GABA sensitivity. Our hypothesis is that if the EEG changes with BZD, namely, spikes disappear with the appearance of fast rhythms,[2] this would indicate a sensitivity to the BZD group. Similarly, electrical non-responsiveness would indicate resistance to BZDs and the choice of a non-GABAergic medication may be more rational. This study aims to determine the electrical signature of "BZD," and how BZD sensitivity testing might be utilized to determine potentially useful antiepileptic drugs, by evaluation of a) the immediate BZD sensitivity test result, and b) the change that has occurred in maintenance AED and rescue medication usage.

Methods. This was a retrospective audit conducted on all children over a 3-year period who had BZD sensitivity testing during EEG. There was a total of 76 children with an age range of 29 days to 16 years old (mean age 5.1 years, SD=4.6) and stratified into 4 groups as follows: 19 (25%) were between 29 days and one year old (mean=0.55 years, SD=0.18); 22 (29%) were aged >1 year to 4 years (mean=2 years, SD=0.92), 24 (32%) were aged >4 to 10 years (mean=6.7 years, SD=1.7), and 11 (14%) patients were aged >10 to 16 years (mean=13 years, SD=2.2). There were 51 (67%) males and 25 (33%) females in this retrospective clinical audit, which in accordance with the NHS UK guidelines, did not require ethical approval. The study was conducted from February 2005 to February 2006, at The Royal Hospital for Sick Children, Edinburgh, Scotland. The Epileptic Syndromic Classification of the patient cohort, according to International League Against Epilepsy details, are shown in **Table 1**.[3] We graded the severity of epileptic episodes according to the seizure frequency as follows: a) 'mild', representing one or more epileptic seizures per year, b) 'moderate', indicating one or more epileptic episodes per month, c) 'severe', one or more episode per week, d) 'refractory responders', daily events that respond to rescue medications, and e) 'refractory non responders', frequent daily seizures with marked unresponsiveness to emergency medications. An intravenous cannula is inserted prior to EEG recording and preferably before the child enters the EEG department. Silver/silver chloride electrodes are used with a conventional 10-20 system and routine baseline recording is made. Diazepam is administered slowly and intravenously, and the effect monitored. An initial dose of 0.2 mg/kg may require a further additional intravenous bolus of 0.1mg/kg.[1] Alternative routes for the administration of BZD include rectal, intranasal, or buccal administration. For the rectal route, a similar dosage is used to that given for the intravenous test. For the intranasal or buccal route, the intravenous solution of midazolam is used in a dose of 0.1-0.2 mg/kg. This is administered slowly and in all cases follows a routine pre-test baseline EEG recording. Full cardiovascular resuscitation equipment is available in the EEG recording room, and the test dose is administered by the medical staff in all cases. In this cohort no child required resuscitation, and no untoward CNS side effects were encountered. Details of the procedures were explained in advance to the parents, or guardian, and if appropriate, to the child. In this cohort, 62 (81%) of children had their BZD test administered intravenously, 9 (12%) were given intranasal midazolam, 3 (4%) buccal midazolam, and 2 (3%) rectal diazepam. For each test recording the following was determined: duration (minutes) of BZD administration, symmetry of the electrical background activity, and duration (minutes) of BZD electrical effects (abolition or reduction in spike number, an increase in the fast rhythm). The sensitivity to BZD was graded as follows: complete response (CR), where the spikes are completely abolished for the remainder of the EEG record, and with the appearance of beta activity through all brain regions. Intermediate response (IR), where the spike number and amplitude is reduced but without complete abolition of spike activity. Likewise, the appearance of beta waveform is variable and may be seen focally or on the unaffected side. An IR is usually time-limited and not sustained to the end of the EEG record. Absence of response (AR), where there is no change in spike amplitude or number and no evidence of fast rhythms. Paradoxical response (PR), in which the amplitude and number of spikes are increased following a BZD, with a variable increase in beta rhythm. The rating scale for clinical improvement was considered as:

Table 1 - Epileptic syndromic classification.

Epileptic diagnosis	Type of epilepsy	No. of cases (%)
Symptomatic and probably symptomatic focal epilepsies (n=46 [60.52%])	Specific focal pathology	9 (20)
	Post infectious	12 (26)
	Migration disorder	4 (9)
	Periventricular leukomalacia	1 (2)
	Associated with chromosomal abnormalities, one multiple mosaic disorder, one chromosome 6 deletion	2 (4)
	Volume loss	15 (33)
	Volume loss with myelination disorder	3 (6)
Epileptic encephalopathies (n=12 [15.70%]) (in which the epileptiform abnormalities may contribute to progressive dysfunction).	West syndrome	6 (50)
	Lennox-Gastaut syndrome	2 (17)
	Other epileptic encephalopathies	2 (17)
	Landau-Kleffner syndrome	1 (8)
	Myoclonic astatic epilepsy	1 (8)
Idiopathic focal epilepsies of infancy and childhood (n=2 [2.63%])	Benign rolandic epilepsy with centro temporal spikes	2 (100)
Idiopathic generalized epilepsy (11 [14.47%])	Polymorphic seizures	8 (73)
	Complex absence	3 (27)
Other types defined by location and etiology (5 [6.57%])	Partial seizures	3 (60)
	Complex partial seizures	2 (40)

definite improvement (DI), where the clinical epileptic episodes resolved completely over a 2-3 week period following the change in the AEDs, along with a marked improvement in the child's general clinical state. Partial improvement (PI), where there was a clear decline in the number of clinical epileptic fits and some improvement in the general clinical condition of the child within 2-3 weeks from alteration of the AED drug regime. No improvement (NI), where the frequency of the clinical epileptic fits and the child's general condition remained unchanged a minimum of 2 weeks from the revised AED maintenance. Epileptic fit frequency was recorded over a short 2-3 week period following the change in AEDs, that in most included the addition of BZD or GABAergic drugs to the child's original AED regimen. Although this is a relatively short interval, children who had undergone BZD sensitivity testing were those who had presented with an acute exacerbation of epileptic fits, and after testing and AED change, any alteration in fit control was readily observed. This clinical follow-up period could have been extended in those with a good response. In those with a poor response, however, follow-up was limited because of the clinical necessity to attempt better seizures control for these children. Emergency medications, which had been used prior to BZD sensitivity testing were recorded with any alteration in the rescue medications following the BZD sensitivity test. Details of the patients pre-test rescue medications are given in **Table 2**. All descriptive statistics were calculated using Microsoft Excel 2002 SP-2 and a Web-based calculator was used in Chi square tests.

Table 2 - Rescue medications before and after testing (n=76).

Rescue medications	No. of cases (%)
Type of rescue before testing	
Benzodiazepine	42 (55.3)
No rescue	22 (28.9)
Paraldehyde	5 (6.6)
PARA + BZD	7 (9.2)
Types of change in rescue after testing	
BZD before and after	35 (48.7)
BZD change to PARA	4 (5.3)
BZD to nil	2 (2.6)
Not available	1 (1.3)
No rescue	15 (23.7)
Nil to BZD	7 (9.2)
PARA before and after	2 (2.6)
PARA to BZD	3 (3.9)
PARA + BZD	4 (5.3)
BZD	3 (3.9)

PARA - paraldehyde, BZD - benzodiazepine

Results. The frequency of epileptic seizures in our cohort is based on the long-term seizure frequency pattern over a one-year period, 2 were mild, 18 were moderate, 31 were severe, 16 were refractory, and 9 were intractable. All patients in the cohort have either undergone BZD testing prior to commencing initial treatment after diagnosis, or later had BZD sensitivity testing to investigate periods of resistant epilepsy that were not responsive to the child's current treatment. Because of episodic intractable seizures in some patients, BZD sensitivity testing was undertaken on more than one occasion (maximum 3). The EEG background

Table 3 - Antiepileptic drugs pre benzodiazepines (BZDs) testing.

Type of AED at time of testing	Abbreviations	No of cases (%)
Single AED		26 (34.2)
Nitrazepam	NZ	4
Clonazepam	CLN	1
Sodium Valproate	SV	7
Phenobarbitone	PB	3
Phenytoin	PHT	9
Carbamazepine	CZ	1
Lamotrigine	LTG	1
Two AEDs		24 (31.6)
Phenobarbitone + Nitrazepam	PB + NZ	1
Valproate + Nitrazepam	SV + NZ	1
Valproate + Clobazam	SV + CL	2
Lamotrigine + Clobazam	LTG + CL	3
Phenytoin + Nitrazepam	PHT + NZ	1
Phenytoin + Phenobarbitone	PHT + PB	4
Carbamazepine + Vigabatrin	CZ +VG	1
Carbamazepine + Phenobarbitone	CZ + PB	1
Lamotrigine + Valproate	LTG + SV	4
Carbamazepine + Valproate	CZ + SV	2
Phenytoin + Valproate	PHT + SV	1
Phenytoin + Ketogenic Diet	PHT + Ketogenic Diet	1
Topiramate + Valproate	TOP + SV	1
Lamotrigine + Topiramate	LTG + TOP	2
More than 2 AEDs		12 (15.8)
Valproate + Lamotrigine + Clobazam + Phenytoin	SV + LTG + CL + PHT	2
Phenytoin + Vigabatrin + Clobazam	PHT + VG + CL	2
Phenytoin + Valproate +Carbamazepine+ Clobazam	PHT + SV + CZ + CL	2
Lamotrigine + Clobazam + Vigabatrin	LTG + CL + VG	2
Carbamazepine + Clobazam + Lamotrigine	CZ + CL + LTG	1
Carbamazepine +Valproate + Clobazam	CZ + SV + CL	1
ACTH + Clobazam + Topiramate	ACTH + CL + TOP	2
No AED		14 (18.4)

AED - antiepileptic drugs, BZD - benzodiazepine

activity in the children in our cohort was abnormal in 63 (82%) cases. Nineteen out of 76 (25%) had symmetrical rhythms slower for age, and 9 (12%) had a background of generalized (virtually encephalopathic) slowing. A further 14 (18%) patient records had background EEG rhythms that were asymmetrical, while 21 (28%) had background activities that were dominated by high amplitude spikes and waves. Spike and wave activity in the pre-BZD test interictal EEG was continuous, namely, in all pages of the EEG record in 22 (29%) patient records, and showed predominantly generalized spikes/poly spikes with slow waves. Nine (12%) patients had EEGs with generalized spikes/ poly spikes limited to 20% of the recording. Twenty-one (28%) of the EEG records had continuous spikes/poly spikes, which were focal and seen throughout the record. Twenty-two (29%) records contained intermittent focal spikes/poly spikes, limited to approximately 20% of the total EEG recording (namely, 5 out of 20 pages). The pre-BZD test EEG captured a clinical epileptic fit during the recording with associated electrical abnormalities in 32 (42%) of the records. The AED therapy combinations prior to BZD testing are seen in **Table 3**. Examining the changes in the overall seizure control of the cohort, based on seizure frequency, we found that 21 (28%) cases fitted the criteria for DI, namely, where the clinical epileptic fits resolved completely over the subsequent 2-3 weeks, along with marked improvement in the child's clinical state. Twenty-four (32%) fitted the category for PI where there was a clear reduction in the number of clinical epileptic episodes and some improvement in the general clinical condition 2 weeks from alteration of the medication, and a further 27 (36%) of cases showed NI in the frequency of the clinical epileptic episodes and the general condition was unchanged 2 weeks later, (4 cases were unavailable). Complete response (CR) with

Table 4 - Different EEG electrical response combined with clinical outcome.

Type of EEG response	Total no. of cases (%) excluding clinically no available response	Definite improvement n (%)	Partial improvement n (%)	No improvement n (%)	Total recovery DI + PI %
Complete response	16 (21.1)	12 (75.0)	3 (18.8)	1 (6.3)	94
Intermediate response	46 (60.5)	7 (15.3)	20 (43.5)	19 (41.3)	58.8
Absence of response	7 (9.2)	2* (28.8) 1 (14.3)	2 (28.6)	3 (42.9)	42.9
Paradoxical response	3 (3.9)	0	0	3 (100)	0
Total	**72 (94.7)**	**21**	**25**	**26**	

*Unsuccessful rectal diazepam administration namely false negative absent electrical response.
DI - definite improvement, PI - partial improvement

total abolition of spikes with widespread beta activity throughout all brain regions was seen in 17 (22%) cases with the following clinical responses: DI = 12 (70%), PI = 3 (18%), NI = 1 (6%) and NA = 1 (6%). Clinical seizure control in those patients where the EEG showed an IR, total number 48 (63%) cases, 7 (15%) had unequivocal DI in clinical seizures control, 20 (43%) had partial clinical seizure control (PI), and 19 (41%) showed unchanging clinical seizure control (NI). The clinical seizure control in patients with an AR revealed 8 cases (11%). Clinical outcome was unavailable in one case. Two of the remaining 7 cases had DI, and 2 had PI in clinical seizure control. Three showed NI in clinical seizure control. In the 3 patients who had a paradoxical EEG response (PR), the amplitude or number of spikes on the EEG increased following BZD testing and there was a variable increase in background beta rhythms. All 3 (4% of the total group) showed NI in their clinical seizure control, but no worsening of clinical seizure control was recorded using our chosen clinical criteria. The overall seizure control in 72 patients following modification of their background AEDs (undertaken in response to the result of BZD testing) is seen in **Table 4**, and shows a highly significant (p<0.001) chi square test relationship between the presence of a complete electrical response to BZDs, and better seizure control following adjustment of medication. Four grades of beta waveform responses were classified according to their locality and their relationship to spikes: 'grade 1' - 35 (45%) patients showed the appearance of beta activity distributed equally throughout all EEG leads, 'grade 2' - 17 (24%) cases showed fast rhythms confined to the areas where there was no spike activity pre-test (namely, remote from the spike foci), 'grade 3'- 13 (17%) cases were seen where the beta activity occurred at the focal spike sites, but also occurred in other remote areas, and 'grade 4' - 11 (14%) cases showed no fast rhythms. The distribution was evenly distributed in 35 (46%), beta activity remote from spike sites in 17 (22%), absent fast rhythms in 11 (15%), and beta waves that had occurred both at focal spike sites and in other remote areas in 13 (17%). A better clinical seizure response occurred when there was strong global beta waves activity (p<0.01). In those cases (24%) where the beta waves occurred remotely from the spikes focus, the major beta activity occurred within equivalent cortical regions in the contralateral

Table 5 - Cases of fast rhythm remote from spikes sites combined with antiepileptic medications (AEDs) before and after testing, listed with pathological finding and clinical outcomes.

Case no.	Pathological diagnosis	Spikes waves distribution pre testing	Predominant beta response in contra lateral hemispheric region	Clinical outcome
8	Post ECHO virus encephalitis	Left hemisphere	Right hemisphere	Partial improvement
12	Pathology associated with Sturge-Weber syndrome on right hemisphere	Phase reversing spikes right post temporal	Left temporal	No improvement
17	Tuberous sclerosis	Right sided	Left sided	Partial improvement
20	Cystic encephalomalacia	Right hemisphere	Left parasagittal	Partial improvement
24	Dilated ventricles with meningoencephalitis	Left Centro temporal	Right sided	Not available
26	Focal area of dysplasia	Post leads	Maximum anteriorly	No improvement
27	Insult to posterior hemisphere	Post leads	Maximum anteriorly	Partial improvement
29	Schizencephaly (midline defect)	Right and left temporal occipital	Maximum frontally	No improvement
35	Meningoencephalitis	Right fronto temporal	Left hemisphere	No improvement
36	Meningoencephalitis	Right sided	Left sided	Partial improvement
51	Focal ischemic areas	Left sided posterior quadrant	Right sided frontally	Partial improvement
52	Tuberous sclerosis	Left post quadrant	Right temporal	Partial improvement
53	Focal ischemic areas	Right sided frontally	Left sided frontally	No improvement
55	Right porencephalic cyst	Right post quadrant	Left frontally	Partial improvement
57	Right hemispherectomy	Right temporal	All over the left hemisphere	Partial improvement
59	Brain atrophy	Posterior region	Frontal region	No improvement
60	Right sided intraventricular hemorrhage	Right post	Left fronto-central	Partial improvement

ECHO - enteric cytopathic human orphan virus
Summary of clinical outcomes: PI - partial improvement (N=10 [58.8%]), NI - no improvement (N=6 [35.3]), NA - not available (N=1 [5.9])

hemisphere. **Table 5** shows the pathological diagnosis, spike sites, and the distribution of fast rhythms along with their clinical outcomes.

Discussion. To make an informed decision on the prescription of a BZD rescue medication, ideally one should know if the individual child will be sensitive to it in everyday situations. The rationale, therefore, for BZD sensitivity testing is that the administration of BZD (via any route under EEG control in children with clinical or electrical seizures), assesses the clinical or electrical response to bolus injection and may guide the clinician in a choice of potentially useful GABAergic rescue and background medication. Pampiglione and Da Costa[4] described how the immediate clinical and electrical response occurred within 30 seconds from intravenous administration of BZDs. Livingston et al[1] reported on the immediate effect of BZD sensitivity testing on 40 children. In 50% of cases, the epileptic activity was abolished and in approximately one third there was no electrical change. He described a paradoxical response in 3 cases and one child who responded positively from non-convulsive status. In 1997, Huang and Shen[5] quantified beta activity after BZD administration, and found that there was significantly less beta activity on the EEG in epileptic patients compared to controls. The principle inhibitory neurotransmitter in the CNS is GABA and is widely distributed throughout the brain. Approximately 60-75% of all CNS synapses are GABAergic. There are at least 3 GABA receptors,[6,7] with at least 5 known mechanisms by which drugs can increase the availability and activity of GABA: i) BZDs increase the frequency and duration of the opening of the chloride ion channel.[8] ii) Release of GABA from glial cells (for example, Gabapentin).[6] iii) Inhibition of GABA transmissions, (for example Valproate in part, works by metabolizing GABA).[6] iv) An increase in GABA synthesis and release (for example Valproate).[9] v) Inhibition of reuptake of GABA by neuron and glial cells, for example, Tiagabine.[6] The common BZDs used in clinical practice include Diazepam, Flunitrazepam, Nitrazepam, Midazolam, Clonazepam, and Oxazepam. Non BZD hypnotics, which act at BZD receptors, include Zolpidem and Zopiclone.[10] Clinical seizures control in our cohort improved by 28% and was accompanied by an improvement in the child's clinical state. This improvement in fit frequency was related entirely to the choice of background anticonvulsant medications following BZD testing. When there was a full electrical response (CR) to BZDs (with abolition of spike activity and widespread beta waves through all brain regions) approximately 3 quarters of the cases were accompanied by a definitive clinical improvement in epileptic seizure control. The post-test medications mostly included GABAergic drugs. An increased dose of the BZDs (in 3 cases) proved effective without altering the background medications. Of this whole group of 17 'CR' children, 10 cases treated with BZDs showed a definite clinical improvement post-test. Two cases showed a partial clinical improvement, and one case showed no clinical improvement. In total, 15 out of the 16 (94%) cases of children who had a full electrical response to testing and known clinical outcome, showed some measure of clinical improvement. The clinical relevance is therefore that BZD sensitivity testing can substantially alter the outcome based on a prediction made at the time of BZD sensitivity testing. Livingstone et al[1] maintained that of those cases with subsequent clinical improvement, 76% of them had had a positive test. Children who had an intermediate type of electrical response to BZDs had a much reduced percentage of clinical recovery. The outcome was evenly divided between definite, partial, and NI for those who had an absent electrical response to testing. Paradoxical response on the EEG to BZD testing occurred in 3 (4%) patients in this cohort (namely, an increase in spike amplitudes and an uncertain amount of fast rhythm). No change was made to their background medications other than a minimal increase in the dose of Nitrazepam in one patient. As might be expected, none of these patients showed any improvement in clinical epilepsy control. This absence of any sort of clinical improvement may be because all these 3 children were on some GABAergic antiepileptic to which they were not electrically responsive. The number however, is very small and a larger series of theses cases with paradoxical electrical response would be useful in understanding the mechanisms of action and as a clinical cue to know which medications to avoid. If fast rhythms (FR - beta waveforms) are seen uniformly distributed throughout all leads, including those areas with previous spike activity in response to administration of BZDs, then these patients show a clear improvement in subsequent clinical outcome, significant at the one percent level.[5] Not all patients with induced FR had this uniform appearance: in some cases the FRs were predominantly seen in the contralateral hemisphere and were noticeably absent from the spike sites. This may indicate an absence of GABA receptor in those spike areas as a result of acquired or congenitally deficient receptors. The clinical responsiveness in this group is very much more measured and most had only a partial clinical improvement. It is possible that these BZDs insensitive areas may provide a guide during electrical corticography to the extent of epilepsy surgery. Consistent with this trend is the absence of any clinical improvement in those patients with no FRs visible after BZD administration. A further pattern of beta responses was seen in 13 patients where the induced beta waves occurred sometimes at focal spike areas, and

at other times in temporarily changing remote areas. In this pattern, 11 of the 13 patients (84%) did show improvement to some extent in the clinical seizure outcome, again confirming that both the quantity of beta wave response and the distribution of that response, will reflect subsequent epilepsy control. This is in accord with other observers.[5] Accepting there is a need for rescue medication in epileptic patients with problematic seizure control, our cohort have had their rescue medication maintained, altered or withdrawn as a result of the sensitivity testing. Two thirds continued with BZDs alone. Approximately one quarter (24%) of patients managed without rescue medication. Small numbers were maintained on rescue medication in addition to a BZD. Forty-five percent had undergone some alteration in the background antiepileptic medications as a result of sensitivity testing. The limitations to this study include its retrospective design, the limited numbers of children having BZD testing available to study, and the restricted duration of follow-up.

This audit study has reinforced the clinical practice of neurologists and shown the predictive value of seizure control based on responsiveness to GABAergic drug administration. Given that BZD testing is a common clinical investigative technique that provides an immediate guide to antiepileptic therapy in patients whose epilepsy control is brittle, who have frequent changes in their medication, and who require urgent treatment alteration, a future controlled clinical trial of BZD testing, although possible, would be difficult to ethically justify. Its usefulness may also be in determining habituation of GABAergic receptors if repeated testing shows a poorer response. Likewise, with maturation of the anatomical substrate and subsequent neuro-excitatory and neuro-inhibitory transmitters with age, BZD sensitivity testing might explain the responsiveness of different antiepileptic drugs at different stages of development. Its value in determining the extent of a lesion prior to surgical lesionectomy is worthy of further study.

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