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Correlations among Measures of Response to Benzodiazepines in Man

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BOND, A. AND M. LADER. *Correlations among measures of response to benzodiazepines in man.* PHARMACOL BIOCHEM BEHAV 18(2) 295–298, 1983.—A retrospective analysis of five studies using benzodiazepines and one using a benzodiazepine-like drug, zopiclone, and involving 61 subjects in toto was carried out. All used a placebo control and all acute studies incorporated pre-treatment values as well. Eight variables which have previously been shown to be sensitive to benzodiazepine action and which covered a range of physiological, psychological and subjective measures were chosen. Within-subject correlations between drug minus placebo values for these variables were computed to examine relationships between the measures while the subjects were taking benzodiazepines. It was found that closely related measures within system were significantly correlated but other correlations were sparse. However under limited conditions, i.e., several doses of one drug in the same subjects as in the zopiclone study, a consistent pattern of effects was shown across measures, resulting in half of the possible correlations showing statistical significance. A similar pattern was shown in patients after 2–4 weeks treatment with benzodiazepines.

Correlations Benzodiazepines Zopiclone Physiological Psychological Subjective measures

WHEN the clinician administers a drug he seeks a predictable therapeutic effect. Although he is prepared to experiment with the dosage to optimise the balance between wanted therapeutic and unwanted side effects, he expects neither lack of response, exaggerated response nor paradoxical response. Nevertheless, these do happen fairly commonly and efforts have been made to reduce the variability of clinical response by measuring plasma drug concentrations or some correlate of clinical response such as EEG changes with psychotropic drugs. These efforts have only been partly successful or involve more trouble than they are worth.

The anomalous responses obtained with medication may comprise lack of response, total or complete, excessive response e.g. profound hypotension with a beta adrenoceptor antagonist, or an unexpected or even paradoxical response unpredictable from the usual pharmacodynamics of the drug. Thus, variability of response can be quantitative or qualitative.

The benzodiazepines furnish a good example of all these clinical anomalies. Some patients show no response at all at even high therapeutic levels and are then incommoded by side effects such as drowsiness. Others suffer such unwanted effects at surprisingly miniscule dose levels. Qualitatively, the benzodiazepines are accepted as tranquillising, anti-emotion drugs, even anti-aggressive [10] but paradoxical excitement and rage reactions have been reported after consumption of these drugs [2, 7, 8].

Can these anecdotal clinical observations be supported by systematic studies aimed at examining response variability to the benzodiazepines? Almost by definition, paradoxical responses are idiosyncratic, with the implication that they are uncommon. Proper studies would need a large epidemiological framework such as post-marketing surveillance procedures. Variability in quantitative response is much more easily studied needing relatively modest numbers of patients.

However, one question needs to be addressed first. Can an individual be labelled a "hyporeactor" or a "hyperreactor" to a benzodiazepine on the basis of just one measure such as subjective clinical report? If not, that is, if responses do not correlate between systems, then the response system, e.g. subjective, performance, EEG and so on, must always be specified.

In this presentation, we first examine correlations between various measures of benzodiazepine effect in normal subjects undergoing laboratory experiments. Then, some previously published correlations from anxious patients are re-examined. We sought consistency between several main areas of drug effect: (a) subjective, mood scales in normals, symptoms in patients; (b) performance, psychomotor and cognitive tests in particular, and (c) physiological, such as fast-wave activity in the EEG. In addition, plasma concentrations were estimated in the patients.

NORMAL SUBJECTS

Benzodiazepines show a characteristic pattern of action on the EEG: they increase fast-wave (13.5–26 Hz) activity, decrease slow-wave activity (4–7.5 Hz) and diminish the various components of the EEG response, the averaged evoked response (AER). On behavioural tests, impairment is typically clearly demonstrable. The subjects have slower reaction times; poor coordination on simple motor tests; performance also deteriorates on more complex cognitive tasks involving attention, coding, new learning or memory. Subjective effects of the benzodiazepines include reports of feeling drowsy, feeble, muzzy, clumsy, lethargic, mentally slow, dreamy and incompetent. Anxiety may be lessened but one

would not expect appreciable anxiolytic effects in normally calm subjects. Certain "side-effects" such as dizziness and physical tiredness may be complained of.

METHOD

In order to examine correlations in the pattern of these effects which we have noted over several studies, we looked at the data from 6 recent studies. These studies all used normal volunteer subjects.

Doses and Subjects

Acute effects of 5 mg diazepam in 8 subjects. (Bond and Lader, in press). Acute effects of 10 mg diazepam in 12 subjects [3]. Acute effects of 10 mg diazepam in 12 subjects [4]. Acute effects of 5 and 10 mg diazepam, 10 and 20 mg clobazam in 10 subjects [12]. Hangover effects of 0.5 and 1 mg flunitrazepam in 9 subjects [11]. Hangover effects of 2.5, 5, 7.5 and 10 mg zopiclone in 10 subjects [9].

All studies used a placebo control and all acute studies incorporated pre-treatment values as well.

Variables

We selected 8 variables which usually showed statistical significance and gave us a concise profile of benzodiazepine action:

4-7.5 Hz waveband of the electroencephalogram (EEG). This represents slow wave activity from the EEG which was recorded from vertex and left temporal electrodes and analysed through four broad wave band filters, the outputs of which were fed into four analog-to-digital converter inputs of a PDP-12A computer which calculated the mean rectified voltage in each waveband.

13.5–26 Hz waveband of the EEG. This represents fast wave activity, recorded in the same manner.

Reaction time. Simple auditory reaction time to a click of moderate intensity was measured. Thirty-two stimuli were presented and the mean reciprocal was calculated.

Tapping rate. The subject tapped a key as quickly as possible for 60 seconds. The inter-tap interval was calculated.

Digit symbol substitution test (DSST). This is a subtest of the Wechsler Adult Intelligence Schedule involving coding skills. The score was the number of items correct in 90 seconds.

Symbol copying test (SCT). This test measures the motor component of the DSST. The same symbols are used but the subject has only to copy them. The score was the number correct in 90 seconds.

Dizziness. This represented one analog scale (100 mm) from the Bodily Symptom Scale, ranging from absent to very severe.

Mood Factor 1. This is the first factor of the Mood Rating Scale [1] which measures sedation on 9 analog scales. If this score was not available, the score on the scale "Alert–Drowsy" was taken. All 8 of these variables were completed on all except one study [12] which only used 4: RT, DSST, SCT and Mood Factor 1. The individual measures were not always recorded in exactly the same way. Full details can be found in the appropriate papers.

Analysis of Data

Within-subject correlations between drug minus placebo values for the variables were computed to examine relationships between the measures while the subjects were taking benzodiazepines.

RESULTS

Drug-Placebo correlations

Those measures which were closely related within system usually correlated significantly in most studies, e.g. activity in the slow waveband of the EEG correlated significantly with activity in the fast waveband. Psychological tests which were related in their construction also showed a significant correlation e.g. DSST and SCT. Likewise different rating scales showed a relationship e.g. Factor 1 of the Mood Rating Scale measuring Alert-Drowsy correlated significantly with the side-effect of dizziness.

Other correlations did emerge both in isolated studies and on up to 3 studies at once and so the correlations were pooled from all studies using benzodiazepines (nos. 1–5). The correlations were divided into (1) low (5 mg diazepam, 0.5 mg flunitrazepam), (Table 1) (2) high (10 mg diazepam, 1 mg flunitrazepam) doses (Table 1), and (3) all doses (Table 2) and Z-transformed correlations were computed. The lower dose showed slightly higher correlations (i.e. more consistency) on the expected relationships and although the higher dose did display some additional correlations e.g. 4–7.5 with Factor 1 and R.T. with DSST, the only other correlation to be significant over all doses was the number of items completed on the SCT which was negatively correlated with the amount of dizziness felt.

As only a quarter of possible correlations were significant, these relationships were quite disappointing until we looked at the study involving zopiclone. Although zopiclone is chemically not a benzodiazepine, it is otherwise similar e.g. it binds to benzodiazepine receptors. Analysing the data from four doses of this drug in the same way, revealed far more consistency. Again the expected relationships between EEG variables, related psychological tests and ratings emerged but also other correlations were evident. Again the data were pooled for low doses (2.5 and 5 mg), high doses (7.5 and 10 mg) (Table 3) and all doses (Table 2) and Z-transformed correlations were carried out.

Several significant correlations were present. There were relationships between EEG variables and tapping and DSST; between psychological measures—e.g. RT with tapping and DSST; tapping with DSST and SCT; and between the mood factor score and 13.5—26 Hz EEG, tapping, DSST and SCT.

Indeed half of the possible correlations were significant beyond the 5% level. Thus a consistent pattern of effects does emerge under limited conditions i.e., same subjects, several doses of one drug. However, the same dose effect as with the benzodiazepine is present: the low doses resulted in slightly more significant correlations than the high doses.

ANXIOUS PATIENTS

In a clinical study completed some years ago [5] 20 chronically anxious out-patients were entered into a trial of three benzodiazepines (diazepam, chlordiazepoxide and medazepam) compared with a barbiturate (amylobarbitone sodium) and a placebo. Most of the measures listed earlier for the normal subjects were recorded together with skin conductance, pulse rate and pupil size. The psychological measures also included cancellation tests, card sorting, and arithmetic tasks. Clinical ratings comprised the Hamilton

TABLE 1

Z-TRANSFORMED CORRELATIONS FOR DRUG MINUS PLACEBO VALUES ON HIGH AND LOW DOSES OF BENZODIAZEPINES

		High dose							
		4–7.5 Hz	13.5–26 Hz	R.T.	Tapping	DSST	SCT	Dizziness	Mood Factor 1
	4–7.5 Hz		0.56‡						0.42†
	13.5–26 Hz	0.62†							
	R.T.					0.32*		0.38*	
	Tapping								
Low dose									
	DSST						0.59§		
	SCT					0.71§			
	Dizziness	−0.76§							
	Mood Factor 1								0.62†

*$p<0.10$; †$p<0.05$; ‡$p<0.01$; §$p<0.001$.

TABLE 2

Z-TRANSFORMED CORRELATIONS FOR DRUG MINUS PLACEBO VALUES ON ALL DOSES OF BENZODIAZEPINES AND ZOPICLONE

		Total Benzodiazepines							
		4–7.5 Hz	13.5–26 Hz	R.T.	Tapping	DSST	SCT	Dizziness	Mood Factor 1
	4–7.5 Hz		0.59§						
	13.5–26 Hz	0.44‡			0.50‡				
	R.T.		0.35*						
	Tapping	−0.45‡		−0.48‡					
Total Zopiclone									
	DSST	0.43†		0.51‡	−0.45‡		0.64§		
	SCT				−0.58§	0.40‡		−0.33†	
	Dizziness							0.44‡	
	Mood Factor 1	−0.39†			0.42†	−0.47‡	−0.53‡	0.46†	

*$p<0.10$; †$p<0.05$; ‡$p<0.01$; §$p<0.001$.

TABLE 3

Z-TRANSFORMED CORRELATIONS FOR DRUG MINUS PLACEBO VALUES ON HIGH AND LOW DOSES OF ZOPICLONE

		High dose							
		4–7.5 Hz	13.5–26 Hz	R.T.	Tapping	DSST	SCT	Dizziness	Mood Factor 1
	4–7.5 Hz		0.42*		−0.50†	0.44*			
	13.5–26 Hz	0.46*							
	R.T.		0.50†		−0.45*			0.44*	
	Tapping		−0.55†	−0.51†			−0.46*		
Low dose									
	DSST	0.41*	0.48†	0.70§	−0.55†		0.44*		−0.50†
	SCT				−0.69‡				−0.45*
	Dizziness								
	Mood Factor 1		−0.57†		0.48†	−0.43*	−0.60‡	0.61†	

*$p<0.10$; †$p<0.05$; ‡$p<0.01$; §$p<0.001$.

Anxiety Scale completed by the psychiatrist on interview and key symptoms rated by the patients themselves.

Within patient correlations were calculated between the physiological measures which showed significant drug effects and these were high within measures e.g. the P_1–N_1 and N_1–P_2 components of the evoked response had a correlation of 0.77 ($p<0.001$) and the 4–7.5 and the 7.5–13.5 Hz wavebands of the EEG correlated 0.86 ($p<0.001$). There was also some relationship between physiological measures e.g. the number of fluctuations in the skin conductance tracing correlated with some EEG measures (e.g. fluctuations decrease as slow wave activity decreases and fast wave activity increases).

Correlations were also computed between the physiological measures showing drug effects, arithmetic and the ratings. As the mean Hamilton score and the mean patient ratings decreased (i.e. as the patient's symptoms improved), there were corresponding decreases in the amplitudes of the three evoked response components, alterations in the EEG wavebands, a decrease in the number of fluctuations and an increase in the number of sums completed on the arithmetic test. Thus, as the benzodiazepines exert their physiological effects, the patients' rated anxiety decreases, and they perform better on the arithmetic test. Such intercorrelations show an integration of drug effects across the clinical, physiological and behavioural aspects of functioning. In chronically anxious patients therefore these drugs produce physiological effects which are useful indicators of drug action: the less the physiological effect shown, the less the clinical effect obtained.

Is this related to the plasma levels of the drugs? In this study, plasma samples were taken for estimation of the appropriate drug and drug metabolite concentrations [6]. The drugs had been taken for a period of 2–4 weeks each. However, these levels were not related to either behavioural measures or clinical ratings. One of the benzodiazepines studied, medazepam, did show some relationship with physiological effects: the plasma concentrations of medazepam correlated negatively with the amplitude of the P_1–N_1 wave of the evoked response and negatively with the percentage of slow wave activity on the EEG but positively with the percentage of fast wave activity.

DISCUSSION

The general lack of high correlations must be set against the intrinsic reliability of the measures. Relationships between measures cannot be expected to be high if the measures themselves are unreliable. In general, however, the variables which we have presented have sufficiently high reliability—test—retest, for useful inter-variable correlations to be possible.

Within-system correlations were reasonably consistent suggesting reliability of measurement and consistency within areas of evaluation. However, the psychological tests tended not to correlate between areas such as cognitive and psychomotor, suggesting that benzodiazepines might affect such aspects differentially. One possibility concerns the muscle-relaxant effects of the drugs. Subjects may be differentially sensitive to the central and spinal cord effects of the benzodiazepines which would attenuate inter-measure correlations where the measures were sampling different functions. Equally, if the central sites of action of the benzodiazepines are differentially responsive in different individuals, low inter-measure correlations between say, cognitive and memory tasks might result. This is, however, speculation.

Correlations were higher at lower doses than at higher doses although this difference was not marked. It is possible that some "ceiling effect" was distorting the responses at high doses but the drug effects even at high doses were not extreme.

The zopiclone data suggest that under the most highly controlled conditions with several doses of one drug, quite consistent correlations are found. Inter-measure consistency would therefore seem to be attainable, but it is a fragile phenomenon easily lost in more complex drug situations. It is also interesting that the zopiclone study was of residual effects, when fairly steady pharmacokinetics would have been attained.

On repeated dosage in the patients a fairly consistent picture emerged. This might again be related to the simpler pharmacokinetics during steady-state administration.

In conclusion, it appears that correlations between measures within system, such as the EEG, are fairly high. Behavioural measures show less inter-correlation except in special circumstances such as dose-ranging studies. Inter-system correlations are generally low except in patients on repeated dose administration. It is possible that response variability across subjects is sufficiently low to warrant global assessments of responsiveness but many caveats must be entered. Analysis of retrospective data can help in this matter but studies specially designed to examine this question are needed.

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