Treatment of myoclonus with pheneturide

C. D. WARD

From the Royal Hospital, Sheffield

SUMMARY Twenty-one patients with various forms of myoclonus are presented. Phenacemide was given to five patients with considerable benefit to three, but with serious toxic effects in two. Another acetylurea derivative, pheneturide, was given to 19 patients and was well tolerated. Myoclonus was completely or substantially controlled in 12 patients.

The term "myoclonus" may be applied to very abrupt involuntary movements which are neurally determined, asynergic, and arrhythmic. An assortment of involuntary movements share these characteristics but differ in their relationship to movement, relaxation, posture, or sensory stimuli, and in their anatomical disposition (Gasaut, 1968); they may involve parts of muscles, whole muscles, or, more usually, muscle groups. Such movements, collectively termed myoclonus, are seen in a wide variety of pathological conditions (Halliday, 1967) and may often be associated with epilepsy. Lesions at many levels in the nervous system have been implicated, while on occasions (Bradshaw, 1954) no structural pathology may be identified. No single drug has been universally preferable in the treatment of myoclonus but there is good evidence for the efficacy of benzodiazepines. Many different drugs have been shown to be effective in individual cases. Serotonergic drugs are frequently effective in postanoxic myoclonus but are rarely of value in other varieties (Myers, 1975). Phenacemide (Phenurone) has been shown previously to be effective in myoclonus (Bradshaw, 1954), but its toxicity is now regarded as unacceptable. Pheneturide (Benuride) is a closely related acetylurea derivative of much reduced toxicity (Hershon and Parsonage, 1969). The use of this drug in a group of patients with myoclonus has not been reported previously.

Patients and methods

This study concerns 21 patients who had been referred to one neurologist (Dr Peter Bradshaw)

between 1965 and 1976. They had displayed myoclonic jerks and had been treated with phenacemide or pheneturide. Of these patients, 16 were seen personally for review and three responded to a questionnaire. Records of outpatient follow-up were available for one patient who had died and for one who could not be traced. All had given a history of repeated, instantaneous involuntary movements and had reported at least one of the following: sudden jerks of the arms causing objects to fly out of the hands; sudden interruption of gait by shock-like jerks of trunk or legs, causing falls without loss of consciousness; jerks sufficiently severe to interfere with sleep; or jerks severe enough to cause embarrassment in company and to be reported by observers.

Each patient underwent full neurological assessment with special attention to differential diagnoses such as coarse muscle fasciculation, extrapyramidal disorder, and hysteria, and with particular reference to the identification of mental impairment, cerebellar disease, and system degenerations. The presence of jerks was noted during formal tests of motor co-ordination, and the following stimuli were applied in an attempt to provoke jerks: rapid muscle stretch, muscle percussion, pinprick, and loud noises. Routine investigations included: urinalysis, full blood count, erythrocyte sedimentation rate (ESR), liver function tests, radiographs of chest and skull, and electroencephalography (EEG). Other investigations such as lumbar puncture were carried out as seemed appropriate. Liver function tests were repeated at intervals during treatment.

Five early patients received phenacemide up to 1000 mg daily in divided doses, and 19 patients received pheneturide up to 800 mg daily in divided doses. Those with epilepsy were given additional anticonvulsants. Firstline choices were phenytoin

Address for reprint requests: Dr C. D. Ward, Department of Neurology, Royal Free Hospital, Hampstead, London NW3.

Accepted 13 February 1978

200 mg–400 mg daily and phenobarbitone 30 mg–90 mg daily. If seizures continued the phenobarbitone was replaced by primidone 750 mg–1000 mg daily, and other drugs were used as necessary.

Results

Using simple clinical criteria (Aigner and Mulder, 1960) the patients were separated into three groups whose features are described briefly below. The effect of phenacemide and pheneturide upon the myoclonus is summarised in the Table.

GROUP 1 MYOCLONIC JERKS WITH EPILEPSY AND CEREBELLAR ATAXIA (CASES 1–4)

One female patient who was born prematurely had had nonprogressive symptoms since early life. She was mentally defective and had a moderate cerebellar ataxia. Myoclonic jerks occurred at random, sometimes causing her to fall. She also had occasional "absence" and grand mal seizures. The EEG showed generalised 3/s spike and wave discharges. Similar clinical features have been reported to follow perinatal hypoxia (Lance, 1968). Phenytoin, primidone, carbamazepine, and sodium valproate in various combinations had no effect

on the jerking although partial control of the seizures was achieved. Pheneturide produced some effect on the myoclonus but this was neither pronounced nor sustained, and was complicated by the precipitation of mild anticonvulsant toxicity.

Three patients had a combination of grand mal epilepsy, slowly progressive cerebellar ataxia, and myoclonic jerking which was always provoked by action and relieved by rest. In case 2, a male aged 21 years, jerks interrupted all attempted movements including speech, and he was often thrown to the ground. His symptoms began at 10 years of age, worsening rapidly up to 17 years and then more slowly. Similar but milder symptoms had begun in another male patient at 29 years, and in a female patient at 14 years. The jerking and ataxia had slowly increased over periods of 37 years and 19 years respectively. All these patients were mentally normal. None had a relevant family history. They conformed, nonetheless, to the clinical syndrome of dyssynergia cerebellaris myoclonica (Hunt, 1921), as defined in a recent review (Roger *et al.*, 1968).

In all these patients other anticonvulsants had been used for a number of years before the introduction of acetylureas and various regimes (Table)

Table Treatment of myoclonus with acetylurea drugs

Case	Type of myoclonus	Daily dosage	Duration of treatment	Clinical benefit	Unwanted effects	Other drugs used concurrently
Phenacemide						
3	Action	750 mg	8 weeks	C	Nausea	Phenytoin
4	Action	750 mg	4 weeks	A	Hepatotoxicity	Phenytoin
5	Random	750 mg	3 years	A	SLE*	Phenobarbitone
6	Stimulus	750 mg	4 years	A	Nil	Nil
Pheneturide						
1	Random	800 mg	2 years	C	Anticonvulsant toxicity	Phenytoin, primidone, valproate, carbamazepine†
2	Action	600 mg	4 years	B	Nil	Phenytoin, phenobarbitone
3	Action	200 mg	4 weeks	C	Drowsiness	Diazepam
4	Action	600 mg	3 years	A	Nil	Phenobarbitone, ethosuximide
6	Random	800 mg	8 weeks	C	Drowsiness‡	Meprobamate
7	Random	600 mg	2 years	C	Nil	Phenytoin, phenobarbitone, primidone, carbamazepine†
8	Random	300 mg	3 years	A	Nil	Nil
9	Random	300 mg	4 years	B	Nil	Phenobarbitone
10	Random	600 mg	2 years	A	Nil	Phenobarbitone
11	Random	600 mg	3 years	C	Nil	Nil
12	Random	600 mg	1 year	A	Nil	Phenytoin
13	Random	300 mg	1 year	A	Nil	Phenytoin
14	Random	600 mg	2 years	C	Nil	Phenytoin
15	Random	600 mg (300 mg)	1 year	A	Skin eruption (dose reduced)	Nil
16	Random	600 mg	6 years	B	Nil	Nil
17	Random	600 mg	6 years	B	Drowsiness‡	Nil
18	Relaxation	300 mg	2 weeks	X	Exacerbation	Nil
19	Action	600 mg	3 years	B	Drowsiness‡	Nil
20	Stimulus	800 mg	4 weeks	A	Nil	Nil

A = control complete or near complete; B = control incomplete but sustained; C = benefit unsustained, doubtful or undetectable; X = deleterious effect on jerking.

*Systemic lupus erythematosus.

†Stated drugs used in various combinations during pheneturide treatment.

‡Symptom not volunteered by patient.

had resulted in complete or near-complete control of seizures without influencing the myoclonus. Pheneturide 600 mg daily improved the myoclonus in case 2 to a dramatic extent initially, but four years later 800 mg was required, and the effect was less marked. Other treatment, including nitrazepam, was ineffective. Phenacemide 750 mg daily markedly reduced the jerking in another patient but the drug was withdrawn one month later after evidence of liver damage. Much later, pheneturide 600 mg daily was equally effective and no hepatotoxicity resulted from three years' treatment. In case 4 neither benzodiazepines nor other drugs influenced the jerking.

GROUP 2 MYOCLONIC JERKING WITH EPILEPSY ONLY ("MYOCLONUS EPILEPSY") (CASES 5-14)

In three of these patients symptoms had begun in early life and of these one had a family history of epilepsy. One patient had exclusively grand mal seizures, one had "absences", and one had a combination of both. In one patient the myoclonus occurred mainly on relaxation either in a chair or in bed, while in the other two the jerks occurred at random. Electroencephalography showed generalised irregular 2-4/s spike and wave discharges in one and regular 3/s spike and wave in another. Symptoms had continued for many years in these patients without remission. Anticonvulsants only partially controlled the seizures. In one patient phenacemide was highly effective in controlling the jerking for three years when it was withdrawn after the development of systemic lupus erythematosus. Nitrazepam and diazepam were of little value in this patient.

In a further seven patients symptoms began in the second decade of life, and were milder. Two who had been followed into the third decade of life had been in remission for three or more years. Family histories of epilepsy were present in four of the seven patients. In two patients the jerking preceded the first seizure by several months. In all, the myoclonus occurred at random apart from an increased frequency in the two hours after waking, and in women during menstruation. In some patients a series of jerks built up over many hours, culminating in a major seizure. All had occasional grand mal seizures except one who had "absences" only. Six EEGs showed generalised irregular 2-4/s spike and wave discharges. Standard anticonvulsants generally controlled the seizures satisfactorily but appeared to have little effect on the jerking. Pheneturide was highly effective in controlling the jerks in five patients.

GROUP 3 MYOCLONUS ALONE (CASES 15-21)

Case 15 was a girl aged 14 years whose brother

had myoclonus epilepsy and whose father had a mild relaxation myoclonus. Her EEG showed polyspike and wave discharges. Her myoclonus was most severe in the early morning and during menstruation, but otherwise occurred at random. She might thus have been included in group 2 except that no seizure had occurred since the onset of jerking one year previously. The myoclonus was very effectively suppressed by pheneturide 600 mg daily. After the onset of a mild skin eruption the drug was withdrawn and the jerks recurred. Nitrazepam was less effective. Pheneturide was then reintroduced in a lower dose without recurrence of the eruption, but with reduced effect on the myoclonus. Case 16 suffered random myoclonus which began shortly after measles vaccination. Jerks coincided with spike and wave EEG discharges. In two other patients, one with random and one with action myoclonus from childhood, without family history, no aetiology could be established. In all these patients substantial control of jerking was achieved with pheneturide.

Case 18 had suffered violent jerking of the legs from the age of 30 years. This occurred solely when he was relaxed either in a chair or in bed. His condition could be distinguished from that of the "restless legs" syndrome (Ekblom, 1960) by the fact that jerks could be suppressed either by mental concentration or by active movement, and by the absence of associated abnormal sensations. Family history was negative and the EEG was normal. Pheneturide exacerbated the symptoms while nitrazepam was of slight benefit only.

In two patients jerks were provoked by sensory stimuli. Case 20 was a previously healthy girl aged 18 years in whom jerking began some days after a mild upper respiratory tract infection. Very frequent, massive, violent myoclonic jerks involved the trunk and limbs, often throwing her from the bed. Various sensory stimuli such as pinprick, sudden noise, and muscle percussion provoked massive jerks. They were not present during sleep. Voluntary movements such as walking produced a great reduction in jerking, and there was no ataxia. Sensation and cortical function were preserved. Amylobarbitone, troxidone, chlorpromazine, and phenobarbitone had all proved ineffective. Within six hours of beginning treatment with pheneturide 600 mg daily, jerks were dramatically reduced, and in 24 hours they were abolished. The drug was discontinued one month later and there was no recurrence of jerking. Lumbar cerebrospinal fluid and EEG were obtained when jerks had abated sufficiently, and these showed no abnormalities. A viral encephalitis was postulated but never proved.

Case 21 developed myoclonus insidiously from the age of 54 years, and was admitted to hospital during an acute relapse. The clinical features were similar to those of case 20. Investigations including EEG were non-contributory. Phenacemide 750 mg daily led to an almost total abolition of jerks within 36 hours although he continued to have milder jerking from time to time. There was no neurological deterioration up to the time of his death from myocardial infarction four years later. No aetiology could be established with certainty.

Discussion

The 21 patients presented here displayed various types of myoclonic jerking. Myoclonus occurring at random was usually worse in the early mornings and during menstruation. This type of myoclonus was usually associated with mild, non-progressive epilepsy, and in the one patient who had suffered no seizures there was good evidence of an inherited epileptic state. Pheneturide was often effective treatment in random myoclonus. Relaxation myoclonus was reported by one epileptic, and "nocturnal myoclonus" has been regarded as an epileptic variant (Symonds, 1953). In one other patient here reported with relaxation myoclonus, however, there were no epileptic features. His symptoms had more in common with the jerking frequently experienced before normal sleep (Oswald, 1959), although his jerking was confined to the legs, perhaps suggesting a disorder at spinal level. Pheneturide was ineffective here. "Stimulus" myoclonus may be confused with "action" myoclonus but in the two examples presented voluntary movements clearly alleviated the jerking. This type of myoclonus may originate from a subcortical disorder (Halliday, 1975), and in the present cases there was no evidence of widespread cortical disease. Stimulus myoclonus responded dramatically to phenacemide in one patient and to pheneturide in the other. Action myoclonus is the most clearly defined variety (Castaigne *et al.*, 1968). In the present patients sensory stimuli failed to provoke jerks. Action myoclonus is characteristic of dyssynergia cerebellaris myoclonica (Roger *et al.*, 1968) and may also follow cerebral anoxia (Lance and Adams, 1963). Pheneturide effectively controlled the jerking in three of four patients with action myoclonus.

The results presented here indicate that acetylurea drugs may be effective in the treatment of various types of myoclonus. The efficacy of phenacemide in five patients confirms a previous report (Bradshaw, 1954), but serious complications ensued in

two patients. The use of pheneturide in myoclonus has not been reported previously. This drug produced unequivocal improvement in 12 of 19 patients with myoclonus of various types and aetiologies. In six patients pheneturide was used alone with very good effect. In other patients the possibility that benefit resulted from inhibition of metabolism of other anticonvulsants cannot be excluded but is unlikely since other drugs had not improved the myoclonus when used alone. Pheneturide was well tolerated by all patients. The most serious toxic reaction was a transient skin eruption. There was no evidence of hepatotoxicity, and pheneturide was safely used in one patient in whom phenacemide had caused liver damage. Mild clinical anticonvulsant toxicity was provoked in one patient. Four patients, on questioning, reported drowsiness insufficient to warrant withdrawal of the drug. From the point of view of toxicity, therefore, there seems no reason why pheneturide should not be considered occasionally as an alternative to a benzodiazepine. In one comparative study of the use of pheneturide and diazepam in epilepsy, pheneturide produced fewer untoward reactions than did diazepam (Hershon and Parsonage, 1969).

Conclusion

The present report is uncontrolled and no valid comparison can be made with other treatment. However, the safety and efficacy of pheneturide in the treatment of myoclonus has been demonstrated, and the use of this drug in selected cases can be recommended.

My thanks are due to Dr Peter Bradshaw for allowing me to examine patients under his care and for advice on the preparation of this paper.

References

- Aigner, B. R., and Mulder, D. W. (1960). Myoclonus—clinical significance and an approach to classification. *Archives of Neurology (Chicago)*, **2**, 600–615.
- Bradshaw, J. P. P. (1954). A study of myoclonus. *Brain*, **77**, 138–157.
- Castaigne, P., Cambie, J., and Escourelle, R. (1968). Les myoclonies d'intention et d'attitude. *Revue Neurologique*, **119**, 107–120.
- Ekbom, K. A. (1960). The restless legs syndrome. *Neurology (Minneapolis)*, **10**, 868–873.
- Gastaut, H. (1968). Séméiologie des myoclonies et nosologie analytique des syndromes myocloniques. *Revue Neurologique*, **119**, 1–30.
- Halliday, A. M. (1967). The clinical incidence of myoclonus. In *Modern Trends in Neurology*, Vol. 4, pp. 65–105. Edited by D. Williams. Butterworth: London.

- Halliday, A. M. (1975). The neurophysiology of myoclonic jerking. In *Myoclonic Seizures*. Excerpta Medica International Congress Series No. 307, pp. 1-29.
- Hershon, H. I., and Parsonage, M. (1969). Comparative trial of diazepam and pheneturide in the treatment of epilepsy. *Lancet*, **2**, 859-862.
- Hunt, J. R. (1921). Dyssyheria cerebellaris myoclonica: primary atrophy of the dentate system: a contribution to the pathology and symptomatology of the cerebellum. *Brain*, **44**, 490-538.
- Lance, J. W. (1968). Myoclonic jerks and falls: aetiology, classification and treatment. *Medical Journal of Australia*, **1**, 113-120.
- Lance, J. W., and Adams, R. D. (1963). The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. *Brain*, **86**, 111-140.
- Myers, G. J. (1975). The treatment of myoclonus. In *Myoclonic Seizures*. Excerpta Medica International Congress Series No. 307, pp. 121-160.
- Oswald, I. (1959). Sudden bodily jerks on falling asleep. *Brain*, **82**, 92-103.
- Roger, J., Soulayrol, R., Hassoun, J., and Gastaut, H. (1968). La dyssynergia cerebellaris myoclonica—maladie de Ramsay Hunt. *Revue Neurologique*, **119**, 85-106.
- Symonds, C. P. (1953). Nocturnal myoclonus. *Journal of Neurology, Neurosurgery, and Psychiatry*, **16**, 166-171.