

A quantitative electrophysiological study of uraemic neuropathy

Diabetic and renal neuropathies compared

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SUMMARY The numbers of functioning motor units and the parameters of the electrically evoked motor unit potentials in the extensor digitorum brevis muscles of 30 patients on chronic haemodialysis for renal failure were obtained using recently introduced quantitative electrophysiological techniques. Measurements of the distal motor latencies and motor nerve conduction velocities in the lateral popliteal nerves of the same patients are also presented. The results support the presence of a “dying back” type of neuropathy in uraemia, with a preferential involvement of the fastest conducting motor axons. Collateral reinnervation and compensatory increase in size of surviving motor units is relatively impaired in uraemic neuropathy in comparison with a similar study on diabetic neuropathy. The significance of paranodal and segmental demyelination in producing abnormalities of conduction velocity in these neuropathies is discussed.

Pathological studies in general support the presence of a primary axonal degeneration with secondary paranodal, and less frequently segmental, demyelination in the peripheral nerves of patients with uraemic neuropathy (Asbury *et al.*, 1963; Dyck *et al.*, 1971; Thomas *et al.*, 1971). Dayan *et al.* (1970) reported segmental demyelination as the main lesion in acute uraemia but in their chronic cases the pathological features were those of predominant axonal damage with secondary changes in myelin morphology. Dinn and Crane (1970), however, found only demyelination, both paranodal and segmental, in their patients.

Electrophysiological studies on peripheral nerves of uraemic subjects have shown only a moderate reduction in nerve conduction velocities (Preswick and Jeremy, 1964; Thomas, 1976) favouring an axonal dysfunction but Thiele and Stålberg (1975) have interpreted the results of single fibre electromyography in these patients as indicating the presence of a predominantly demyelinating lesion. Opinions on the underlying pathological abnormality in the peripheral nerves of patients with uraemic neuropathy remain controversial but the

most consistently reported abnormality is axonal degeneration (Thomas, 1976).

The present study was designed to quantify the electrophysiological changes in uraemic neuropathy in terms of motor unit numbers and the changes in motor unit potential parameters in the extensor digitorum brevis muscles (EDB) of renal patients. The relationships of these parameters to motor nerve conduction velocities and distal motor latencies are presented and discussed in the context of present concepts of the underlying pathophysiological processes at work in this condition. Where pertinent, these results are compared with those we have already reported in diabetic neuropathy (Hansen and Ballantyne, 1977).

Methods

The composition and placement of the surface recording electrodes over the EDB muscle, the properties of the stimulating electrodes over the anterior tibial nerve at the ankle, and the details of the rate and strength of stimulation used to evoke motor unit potentials have been described by Ballantyne and Hansen (1974a). The amplification and display systems, the computer handling of

data for the estimation of motor unit numbers in the EDB muscle, and the computer derivation of the parameters of electrically evoked motor unit potentials have also been reported (Ballantyne and Hansen, 1974a, b).

Briefly, motor unit potentials (MUPs) recorded from surface electrodes over the EDB muscle are sequentially evoked by finely graded incremental stimulation of the anterior tibial nerve at the ankle. Recruitment of up to 15 motor units can be recognised by a combination of visual and computer analysis of the muscle action potential increments displayed on the oscilloscope screen. The first motor unit potential is displayed in isolation on the oscilloscope, the potential of the second is incorporated in a compound muscle action potential containing motor units 1 and 2. As each new potential is added to the preceding one, the compound muscle action potential so constituted is stored in a computer memory (template). Template 1 contains motor unit potential 1, template 2 contains the sum of MUPs 1 and 2, template 3 contains the sum of MUPs 1, 2, and 3, and so on. Up to 15 templates can be stored in this way. The number of motor units in the EDB muscle is calculated from the formula:

$$MUC = \frac{A(M)}{A(N)} \times N \text{ where } A(M) = \text{area of the}$$

supramaximally evoked muscle action potential, and A(N) = the area of the compound muscle action potential containing N motor unit potentials (Ballantyne and Hansen, 1974a).

By a process of template subtraction the computer also displays the first and sequentially recruited MUPs in isolation. For example, subtraction of template 1 from template 2 will reveal motor unit potential 2, subtraction of template 3 from 4 will leave MUP 4 in isolation, and so on. The latencies, durations, amplitudes, and areas of individual MUPs are then measured. Amplitudes and areas are provided by the computer while latencies and durations are measured manually from computer printout (Ballantyne and Hansen, 1974b). All potential recordings in these studies were from surface electrodes over the EDB muscle.

Fastest motor nerve conduction velocities (FMNCVs) in the lateral popliteal nerve (knee to ankle segment), and shortest distal motor latencies (SDMLs) (anterior tibial nerve at the ankle to EDB muscle), were also measured from the same surface electrodes over the EDB muscle. All investigations were undertaken in a thermostatically controlled room and limb temperature maintained at 33°C ± 1°C.

Patients

Thirty patients, aged 38 ± 13 years, were studied, all of whom had been on chronic haemodialysis for five months to 10 years (mean 2.3 years) in the renal unit at Stobhill General Hospital in Glasgow. So far as was possible, no patient who showed evidence of any other disease which might give rise to a neuropathy was entered into the study. The patients were examined for clinical evidence of neuropathy on the basis of subjective or objective peripheral sensory dysfunction and subjective or objective peripheral motor dysfunction. Only four of the 30 patients in the study had definite clinical evidence of neuropathy. There were 22 control subjects, aged 38 ± 14 years, drawn from relatives and staff of the Institute of Neurological Sciences, Glasgow. All control subjects were free from neurological disease.

Results

All the results are expressed as the mean ± one standard deviation. The statistical significances of the results were evaluated using Student's *t* test.

SHORTEST DISTAL MOTOR LATENCIES

The mean shortest distal motor latency (SDML) in the uraemic patients was significantly prolonged over control values (Table 1). The SDMLs were within the normal range in 17 patients and greater than two standard deviations above the mean value of the control subjects in 13.

FASTEST MOTOR NERVE CONDUCTION VELOCITY

The mean fastest motor nerve conduction velocity (FMNCV) in uraemic patients as a whole was significantly reduced compared to the control value (Table 1). Eight of the uraemic patients had FMNCVs within the normal range but in 22

Table 1 Mean age, shortest distal motor latency, fastest motor nerve conduction, and motor unit numbers in uraemic patients and control subjects

	<i>n</i>	\bar{m}	<i>SD</i>	<i>P</i>
Age (yr)				
Control subjects	22	38.2	13.9	NS
Uraemic patients	30	38.0	13.0	
Shortest distal motor latency (ms)				
Control subjects	20	3.43	0.46	< 0.0001
Uraemic patients	30	4.43	0.86	
Fastest motor nerve conduction velocity (m/s)				
Control subjects	20	51.7	3.6	< 0.0001
Uraemic patients	30	40.5	5.9	
Motor unit numbers				
Control subjects	37	196.8	48.8	< 0.002
Uraemic patients	29	126.4	93.7	

patients the values were lower than two standard deviations from the mean control value. There was a significant positive correlation between FMNCVs in the lateral popliteal nerves and motor unit numbers in the EDB muscle in these patients ($r=0.369$; $P<0.05$).

MOTOR UNIT NUMBERS

The mean motor unit number in the EDB muscles of the uraemic patients was significantly less than the control value (Table 1). In 18 patients motor unit numbers were within the normal range while in 12, motor unit numbers were lower than two standard deviations from the mean value for control subjects.

Only seven of the 30 uraemic patients had normal values for all three parameters—that is SDML, FMNCV, and motor unit numbers. In the other 23 patients one or all of these parameters were abnormal.

MOTOR UNIT POTENTIAL LATENCIES

The mean motor unit potential (MUP) latency in uraemic patients was significantly greater than the control value (Table 2). Mean MUP latencies showed a significant negative correlation with FMNCVs ($r=-0.504$; $P<0.01$) and a significant positive correlation with SDMLs ($r=0.706$; $P<0.001$).

DURATION OF MOTOR UNIT POTENTIALS

The mean duration of motor unit potentials in the uraemic patients was significantly less than the mean control value (Table 2). Mean MUP durations showed a significant positive correlation with SDMLs ($r=0.377$; $P<0.05$).

MOTOR UNIT POTENTIAL AMPLITUDES

Mean MUP amplitude in the uraemic patients was

significantly increased above the mean control value (Table 2).

MOTOR UNIT POTENTIAL AREAS

Mean MUP area was significantly increased over the mean control value (Table 2).

Discussion

The quantitative methods used in this study are similar to those we have applied in diabetic neuropathy (Hansen and Ballantyne, 1977). In addition to a discussion of the present findings in uraemic patients we believe it is useful to compare the similarities and differences in the electrophysiological parameters in the two neuropathies.

Fluctuations in nerve conduction velocity values have been reported in uraemic patients (Kominami *et al.*, 1971; Williams *et al.*, 1973). This fluctuation has been attributed to temporal variation in the metabolic disturbance, as yet unidentified, in these patients. The present study was repeated on 25 of the original patients between three and 18 months after the initial investigation. Comparison of the results using a paired *t* test showed no significant differences in FMNCVs, SDMLs, motor unit numbers, or MUP parameters between the first and second set of recordings. It is, therefore, a reasonable conclusion that, at the time of the first investigation on which this report is based, the neurophysiological status of these patients was stable.

AXONAL DYSFUNCTION

There is a significant reduction in the mean number of functioning motor units in patients with uraemic neuropathy. This could be a consequence of either axonal dysfunction or demyelination block to conduction. Demyelination, however, is not associated with anatomical denervation of the muscle fibres, and collateral reinnervation will not occur (Adams *et al.*, 1962; Robert and Oester, 1970).

Surviving motor units in patients with uraemic neuropathy have potentials of significantly greater mean amplitude and mean area than those found in control subjects. As we have discussed previously (Ballantyne and Hansen, 1975; Hansen and Ballantyne, 1977), these changes indicate the presence of an increased number of muscle fibres in each motor unit and consequently axonal dysfunction with collateral reinnervation. This observation is not compatible with a purely demyelination block leading to loss of functioning motor units.

The mean values for these parameters are, how-

Table 2 Mean MUP parameters in EDB muscle in uraemic patients and control subjects

	<i>n</i>	\bar{m}	<i>SD</i>	<i>P</i>
Latency of motor unit potentials (ms)				
Control subjects	160	4.49	0.82	
Uraemic patients	192	5.80	1.48	<0.0001
Duration of motor unit potentials (ms)				
Control subjects	160	9.50	1.70	
Uraemic patients	192	8.87	1.93	<0.002
Amplitude of motor unit potentials (μ V)				
Control subjects	160	58.6	28.5	
Uraemic patients	192	83.0	77.6	<0.0005
Area of motor unit potentials (units of area)				
Control subjects	160	16.5	7.6	
Uraemic patients	192	22.2	21.4	<0.002

ever, significantly less than those we have found in patients with diabetic neuropathy who have a comparable number of surviving motor units (Table 3). These findings suggest that in uraemic

that the MUP area in uraemic neuropathy does not increase to the same extent as in diabetic neuropathy could be explained on this basis. Synaptic failure reducing the amount of collateral reinnervation would also explain the relatively normal muscle fibre densities reported by Thiele and Stålberg (1975) in their single fibre EMG study in uraemic patients.

Table 3 *Electrophysiological parameters in uraemic and diabetic neuropathies*

	<i>n</i>	\bar{m}	<i>SD</i>	<i>P</i>
Shortest distal motor latency (ms)				
Uraemic	30	4.43	0.86	NS
Diabetic	40	4.56	0.99	
Fastest motor nerve conduction velocity (m/s)				
Uraemic	30	40.5	5.9	NS
Diabetic	40	42.2	6.5	
Motor unit numbers				
Uraemic	29	126.4	93.7	NS
Diabetic	35	106.0	70.0	
Latency of motor unit potentials (ms)				
Uraemic	192	5.80	1.48	NS
Diabetic	270	5.70	1.55	
Duration of motor unit potentials (ms)				
Uraemic	192	8.87	1.93	< 0.0002
Diabetic	270	9.66	1.99	
Amplitude of motor unit potentials (μV)				
Uraemic	192	83.0	77.6	< 0.01
Diabetic	270	109.5	127.9	
Area of motor unit potentials				
Uraemic	192	22.2	21.4	< 0.0005
Diabetic	270	32.1	35.9	

neuropathy collateral reinnervation is relatively impaired compared with that found in diabetic neuropathy. This would suggest a more severe axonal dysfunction in uraemic patients, and is in agreement with the report of Asbury *et al.* (1963) who found little pathological evidence of regeneration in the intramuscular nerve fibres of uraemic patients despite marked distal axonal degeneration.

McComas *et al.* (1975) have postulated six stages of axonal degeneration. Stages two and three consist of "partial (restricted)" and "partial (generalised)" synaptic failure, conditions in which impulse transmission at the synapse is impaired or absent and the muscle fibres cannot be activated by stimulation of the motor nerves. Chemical trophic mechanisms from nerve to muscle, however, remain operative so that the muscle fibres do not degenerate and will not accept endplates from the collateral sprouts of adjacent nerve twigs. These muscle fibres will not, therefore, be available for reinnervation. If widespread, this process would reduce the amount of collateral reinnervation occurring in the muscles of these patients with a corresponding reduction in the compensatory increase in size (MUP area) of surviving functioning motor units. The observation

MUP DURATION

Mean MUP duration was significantly reduced in the uraemic patients compared with control subjects. The change in this parameter contrasts with our findings in the neuropathy of diabetes mellitus (Hansen and Ballantyne, 1977) in which mean MUP duration was significantly increased over control values. The positive correlation between the mean MUP duration and SDMLs in uraemic patients indicates that the conduction time in the distal segment of the motor axon and its intramuscular branches is of importance in determining the duration of the motor unit potential (see Ballantyne and Hansen, 1975; Hansen and Ballantyne, 1977 for discussion). Such a relationship is also found in diabetic neuropathy. If, however, we compare the SDMLs in uraemic and diabetic patients they are not significantly different (Table 3), and this suggests that, in addition to variations of conduction velocity in the intramuscular nerve fibres, some other factor or factors are important in producing changes in MUP duration in uraemic patients. Segmental demyelination produces a more marked slowing of conduction velocity in nerve fibres than does axonal degeneration (Gilliatt, 1966, 1973). In the case of diabetic neuropathy in which segmental demyelination is the prominent histopathological feature, it might be anticipated that the more pronounced slowing of conduction velocity induced in the intramuscular nerve fibres would, by accentuating the differences in conduction time through the intramuscular branches of the motor axon, have a further desynchronising effect on the motor unit potential with a consequent prolongation of the duration of that potential. Since segmental demyelination is not prominent in uraemic neuropathy this effect would be small or absent so that the prolongation of the duration of the motor unit potential would not occur. If this is the explanation for the differences in MUP duration between uraemic and diabetic neuropathy we would also expect that shortest distal motor latencies and MUP latencies would be significantly decreased in uraemic neuropathy compared to the diabetic type. This is not, however, the case (Table 3) as the mean SDMLs and mean MUP

latencies in uraemic and diabetic neuropathies are not significantly different. Consequently the presence of more abundant segmental demyelination in diabetic neuropathy does not explain adequately the differences we have found in MUP duration. The shortened duration of the motor unit potential in uraemic patients can, however, be explained on the basis of a "dying back" process affecting the intramuscular nerve fibres as described histologically by Asbury *et al.* (1963) and Thomas *et al.* (1971). This would presumably affect the longest intramuscular nerve fibres most severely. The more marked denervation of those muscle fibres served by the longest intramuscular nerve twigs will lead to loss of the late components of the motor unit potential and consequent shortening of the duration of that potential. This dying back process will have a relatively greater effect on MUP duration than on MUP latency since the latter depends on conduction in the shorter intramuscular nerve twigs of the motor axon. In this circumstance, however, pathological slowing of conduction velocity in the intramuscular nerve fibres, for whatever reason, should continue to influence the duration of the motor unit potential, and this conclusion is supported by the significant positive correlation we have found in our uraemic patients between SDMLs in the lateral popliteal nerves and MUP durations ($r=0.377$; $P<0.05$). Our observations on the motor unit potential duration in uraemic neuropathy would also be compatible with McComas's hypothesis (see above) if synaptic failure were most marked at those endplates supplied by the longest intramuscular nerve fibres.

MOTOR NERVE CONDUCTION VELOCITY AND MOTOR UNIT NUMBERS

There is a significant correlation between FMNCVs and motor unit numbers in uraemic patients. Does this indicate that the slowing of conduction is a simple consequence of loss of functioning motor units? Is there in addition a pathological slowing of conduction in surviving functioning axons? If there is a random process affecting motor axons then progressive reduction in motor unit numbers and functioning motor axons due to axonal degeneration is unlikely to produce the relationship we have found between the FMNCVs and motor unit numbers. This correlation would arise with preferential loss of faster conducting axons of larger diameter, with progressive involvement of the remaining largest axons as the disease progresses. Dyck *et al.* (1971) and Thomas *et al.* (1971) have reported the loss of larger diameter myelinated fibres in their biopsy material

from uraemic patients. It is difficult to avoid the conclusion that a progressive and preferential loss of the larger axons contributes to the proportionality between motor unit numbers and FMNCVs. This is unlikely to be the total explanation of the reduction in conduction velocity. A rapid improvement in conduction velocity in uraemic patients has been reported after haemodialysis and renal transplantation (Bolton *et al.*, 1971) and this suggests the elimination of a fast-acting metabolic factor producing reduction in conduction velocity in still functioning motor axons. It has been suggested (Hollinrake and Thomas, 1968) that this improvement may be related to rapid physicochemical alterations in the paranodal region. Reduction in conduction velocity in the absence of demonstrable pathological changes has also been reported (Sharma and Thomas, 1974). The rapid improvement in conduction velocity after renal transplantation and haemodialysis in some patients has led to the belief that this could not be due to axonal regeneration. If, however, the earliest changes of axonal degeneration manifest themselves as synaptic failure which in the early stages may be a consequence of biochemical rather than physical derangement, then the dysfunction could be rapidly reversible in less severely affected motor axons. The restoration of transmission in a proportion of previously silent endplates innervated by large fast-conducting axons could produce a rapid improvement in the conduction velocity in dialysed patients and those who have had a renal transplant. We have little evidence from our present study that any influence other than reduction in motor unit numbers has produced slowing of motor nerve conduction velocity. We do, however, have indirect evidence of this from our studies of patients with motor neurone disease. In that condition there is also a positive correlation between motor unit numbers and FMNCVs ($r=0.720$; $P<0.001$) (in preparation). For a given number of functioning motor units, the slowing of conduction velocity is considerably greater in uraemic patients than in patients with motor neurone disease. This difference may be a reflection of the presence of an additional factor interfering with peripheral nerve function in uraemic neuropathy and producing pathological slowing of conduction velocity in surviving and functioning motor nerve fibres. Furthermore, in only 12 of our uraemic patients were motor unit numbers reduced to below two standard deviations or normal values while 22 of the 30 patients had FMNCVs more than two standard deviations below control value. This is further evidence for a factor other than

loss of functioning motor units in the reduction of motor nerve conduction.

DEMYELINATION AND MOTOR CONDUCTION VELOCITY IN URAEMIC AND DIABETIC NEUROPATHIES

In uraemic and diabetic neuropathies mean motor unit numbers, mean FMNCVs, mean SDMLs, and mean ages of the patients are not significantly different (Table 3). Both conditions show similar and significant relationships between FMNCVs and motor unit numbers. As we have already discussed, axonal degeneration with secondary paranodal demyelination is the predominant lesion in uraemic neuropathy while diabetic neuropathy shows conspicuous segmental demyelination. Our electrophysiological results indicate that, for a comparable number of functioning motor units in diabetic and renal neuropathies, the slowing of motor conduction velocities and the prolongation of shortest distal motor latencies are similar. In the chronic neuropathies of diabetes mellitus and uraemia the above observations can be interpreted in several ways:

1. Paranodal and/or segmental demyelination produce quantitatively similar effects on motor nerve conduction velocities.
2. Paranodal and/or segmental demyelination are not of primary importance in producing reduction in motor nerve conduction velocity.
3. Paranodal and/or segmental demyelination are relatively less important in reducing conduction velocity in motor nerves than is the reduction in the number of functioning motor units.
4. Paranodal and/or segmental demyelination and a reduction in the number of functioning motor units are interdependent indices of the underlying pathophysiological process in these conditions.

Conclusions

The changes in motor unit potential parameters and the reduction in the numbers of functioning motor units support the presence of a dying back type of neuropathy in uraemic patients. While collateral reinnervation by surviving units occurs—as demonstrated by the increase in mean motor unit potential areas in these patients—this increase is significantly less than that which occurs in comparable circumstances in diabetic neuropathy. This indicates a relatively impaired capacity for collateral reinnervation and compensatory increase in muscle fibre content of surviving units in uraemic neuropathy.

The reduction in motor nerve conduction

velocity is in proportion to the reduction in the number of functioning motor units and is compatible with progressive loss of the large diameter fast-conducting motor axons. From our consideration of the results obtained in diabetic and renal neuropathies it appears that paranodal and segmental demyelination may produce quantitatively similar effects on motor nerve conduction velocity but both neuropathies have in common a significant positive relationship between motor nerve conduction velocities and the number of functioning motor units.

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