Neurological effects of glutethimide

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Thalidomide in its heyday commonly produced neuropathy. The chemical similarity of the frequently used sedative glutethimide (Doriden) to thalidomide prompted Fullerton and Kremer (1961) to say, 'It is interesting that similar toxic effects have not been reported in patients taking glutethimide . . .'. Since this statement, three authors have reported a total of four cases of nervous system damage due to glutethimide (Bartholomew, 1961; Lingl, 1966; Nover, 1967). Bartholomew's two cases had a neuropathy much like that reported with thalidomide. Lingl's case presented with a pronounced cerebellar disorder and an organic mental syndrome. The patient improved considerably after withdrawal of glutethimide, but eight months later was still somewhat ataxic and mentally impaired. Nover's case is re-examined here with a more extensive follow-up (Case 1). We will present three cases in which serious and long-lasting nervous system impairment resulted from the chronic ingestion of glutethimide. A neuropathy similar to that reported with thalidomide was present in all three cases, but the most impressive damage was cerebellar.

CASE REPORTS

CASE 1 E.B., a 42-year-old white woman was a moderate to heavy drinker before 1960 when glutethimide was prescribed as a substitute for the alcohol. The glutethimide substituted successfully, since she abstained totally from alcohol up to the time she came to our clinic on 6 December 1965. However, she took gradually increasing amounts of glutethimide, and for some six months before coming to the clinic she was taking 3 to 4 g/day. She began having trouble walking during this same period and gradually became unable to walk without assistance. Her eating habits had been poor for many months and her weight dropped from her usual 130 lb to 106 lb. For several years she had been taking pills containing vitamin B₁₂, folic acid, and ascorbic acid, but no thiamine.

When seen in the clinic on 6 December 1965, she complained of distal paraesthesiae in all extremities. She had gross cerebellar ataxia that precluded unassisted walking. The heel-shin test was markedly ataxic and dysmetric, and so was the finger-nose test. All stretch reflexes were absent. Sensation was intact. Speech was

dysarthric. Pupils were widely dilated—a common finding in acute glutethimide intoxication. There was horizontal and rotary nystagmus. There were no other noteworthy findings.

While waiting for admission to the hospital, she continued to take glutethimide and on admission to the Syracuse Psychiatric Hospital on 14 January 1966 she showed the above findings with the addition of blunted position, vibration, light touch and pin prick sensibility in all extremities distally.

In the hospital she was very gradually weaned from glutethimide, but had some withdrawal convulsions. She was treated with one multivitamin pill a day, containing 25 mg thiamine. She was discharged slightly improved on 8 March 1966, two months after admission.

Examination six weeks after discharge showed that her gait was still grossly ataxic, although she could walk a little without assistance. Sensation was intact except for dysaesthesiae to touch in the distal upper and lower extremities. Three months after discharge she showed only minimal further improvement. Sensation was now normal. Finger-nose ataxia was minimal. Heel-shin test and gait remained grossly impaired.

A year after admission to the hospital she demonstrated continuing improvement, but still had quite an ataxic gait. Some time after this, improvement ceased, and the last examination on 14 May 1968, about 2½ years after her first visit to our clinic, showed the following. She walked with a slightly unsteady, wide-based cerebellar gait; she could not do tandem walking. There was mild dysmetria on the heel-shin test and minima l ataxia on the finger-nose test. Stretch reflexes remained absent. Sensation was normal except for slightly subnormal vibration sense in the toes. Speech was slightly dysarthric.

After her first hospital admission, she had three more psychiatric hospitalizations for drinking, depression, and the ingestion of meprobamate, promazine, and nortriptyline. During these admissions no deterioration of her neurological state was reported.

EMG and nerve conduction studies were done during her first hospitalization. Coaxial needle electromyography of the anterior tibial muscle showed only a slight excess of large, lengthened polyphasic motor units. Left median nerve conduction velocity (cubital fossa to wrist) was 42 m/sec (normal is 47 m/sec or greater). Terminal latency was normal at 3.5 msec. Surface electrodes over the median nerve at the wrist recorded no sensory action potential while the index and middle fingers were stimulated together (superimposed sweeps were photographed). In similar manner, stimulating the median

nerve at the wrist showed no nerve action potential at the cubital fossa. The peroneal nerve fibular neck to ankle motor conduction velocity was 32 m/sec (normal is 37 m/sec or faster). Terminal latency was normal at 4.5 msec.

CASE 2 R.D., a 45-year-old white woman was an occasional social drinker until a year before admission to hospital, when she began drinking wine habitually (about 1 litre a day), and began taking glutethimide regularly, in a dose of 250 mg t.i.d. But she continued to eat well and remained asymptomatic until the week before admission, when she developed progressive ataxia of gait and confusion, and had hallucinations. During this week she did not alter her wine intake, but she did take a larger dose of glutethimide: her husband noted that the pills diminished rapidly in the bottle.

On admission to the Syracuse Psychiatric Hospital on 27 June 1967 she was alert, but confused and disoriented. Her speech was well-articulated, but frequently incoherent. Cranial nerves were normal (no nystagmus). She could not walk and was very unco-ordinated in her arms and legs. She had frequent gross, purposeless, bizarre movements of all limbs. Power and sensation could not be adequately tested. Stretch reflexes were 1+ in the upper limbs; knee jerks were 2+ and ankle jerks 1+. Plantar responses were flexor.

She soon became more confused and incontinent and was therefore given six electroshock treatments, but without much improvement in her condition. She began to improve by early August, about two months after admission. Vitamin therapy was not begun until 7 September (two multivitamin pills a day). Slow improvement continued, so that by the time of her discharge from the hospital on 12 October 1967, she was no longer psychotic and could walk, but with considerable ataxia. She complained of numbness in both hands for the first time. Skull films, EEG, and lumbar puncture in the hospital were unremarkable.

Neurological examination on 14 November 1967 showed the following. She was intact mentally, but not as bright as expected for her educational achievement. She complained of numbness in her hands and feet. Her gait was wide-based and markedly ataxic. Finger-nose test showed slowness and ataxia. There was mild distal weakness in upper and lower limbs. Stretch reflexes were absent. There was moderate blunting of pin prick, touch, vibration, and position sensibility in her hands and feet.

EMG of the anterior tibial muscle on 8 December 1967 showed an excess of very polyphasic motor units and a decreased interference pattern, but no fibrillations or positive sharp waves. The conduction velocity of the left peroneal nerve was measured in standard fashion and was 31.5 m/sec (normal is 37 m/sec or faster).

She has improved very little since November 1967. Our last neurological examination on 28 May 1968, approximately one year after admission, showed the following. She still complained of numbness and occasional prickling in her fingers and toes. Her gait was wide-based and moderately ataxic—she did not walk well enough to leave her house by herself. Finger-nose

test showed slight ataxia and terminal tremor. Heel-shin test was mildly dysmetric. Strength in her distal limb muscles had become almost normal. She remained areflexic. Touch and pin prick sensation were slightly blunted in the fingers. Vibration sense was moderately blunted in her finger pads, but not at the wrist. Position sense was slightly blunted in the fingers. Touch was intact in the feet. Pin prick was hardly felt in the toes, while in the foot proper she was hyperalgesic. Vibration sense was slightly blunted in the feet. Position sense was normal in her toes.

CASE 3 I.M., a 41-year-old white woman was an occasional social drinker until about one year before admission, when she began to drink cocktails quite regularly. At the same time she began to take about 1 g glutethimide a day for loneliness, worrying, and insomnia. During the two to four months before admission she drank more heavily, but then stopped drinking about one month before admission, when she began to have leg pains, nausea, and occasional vomiting. Neurological examination in this period was unremarkable. She depended on glutethimide alone after she stopped drinking. On the fifth and fourth days before admission she took about 2 g glutethimide a day, and in the next three days took a total of 12 g.

She was brought to St. Joseph's Hospital in Syracuse on a stretcher on 8 December 1966, having been delirious for several days. She was confused, disoriented, delusional and hallucinatory. Her speech was slurred. She could not walk and, although the hospital chart did not give the reason for this, when all the possibilities are considered, cerebellar ataxia seems the most probable explanation. She would not co-operate in having her feet and legs tested. No upper limb ataxia was noted. All stretch reflexes were brisk, including the ankle jerks. Plantar responses were flexor. Pin prick sensation was blunted in patchy fashion in both feet. Cranial nerves were unremarkable except for dilated pupils. The blood level of glutethimide was not measured until four days after admission when it was 0.6 mg% (normal is zero by the method of Korzun and Brody, 1965). She was treated with chlorthalidone and paraldehyde, but no vitamins. Her mental state improved within a week and cleared at the end of two weeks, yet she was not able to walk until the end of four weeks.

She was discharged from the hospital on 7 January 1967, complaining of pains in her legs and burning in the soles of her feet. She was referred to one of us (D.C.H.) for these symptoms and when seen on 8 February 1967, two months after admission to the hospital, she showed the following neurological findings. Although her mentation was intact, she seemed simple-minded for a person with a college education, and she was suspicious and poorly co-operative. Her feet obviously troubled her greatly, for she would not allow her soles to be touched. Both lower limbs were mildly wasted below the knees. All lower limb muscles were slightly weak, but the anterior compartment muscles of the legs were the weakest. Her hands and forearms were slightly weak and slender. There was no upper or lower limb ataxia and her gait was intact. Stretch reflexes were normal in the upper

limbs; knee jerks were 2+ and ankle jerks 1+. Plantar responses could not be tested. Pin prick was quite blunted in the feet but was normal in the hands. All other sensory modalities were normal. Cranial nerves were unremarkable.

The conduction velocity of the left peroneal nerve was measured in standard fashion on 23 February 1967 and found to be normal: 42 m/sec.

She received therapeutic doses of B vitamins for several months after discharge from the hospital. She recovered from her neuritic symptoms several months after her office visit of 8 February 1967.

SUMMARY OF CASES

Cerebellar ataxia, especially of gait, was a striking symptom in all three cases. In the two who also drank alcohol (Cases 2 and 3) the ataxia began about two weeks before hospitalization and progressed rapidly to inability to walk. The non-drinker (Case 1) developed ataxia of gait about six months before coming to our clinic, and, although the ataxia progressed slowly, it reached the same severity. In two cases the ataxia diminished very gradually: Case 2 still had marked ataxia four months after admission to the hospital, and is even now moderately ataxic, almost one year after the onset of symptoms; Case 1 was barely able to walk without help six months after admission to the hospital, and is now still mildly ataxic more than two years after admission. Case 3, on the other hand, recovered from the ataxia more rapidly. All three cases had a mild sensori-motor peripheral neuritis. Although neuritic manifestations were not noted in Case 2 until four months after admission to the hospital, her abnormal mental state and her being on a psychiatric ward may have precluded earlier detection. This patient continues to have mild neuritic symptoms and signs 11 months after her admission to the hospital. The other two cases had lost almost all neuritic manifestations about seven months after admission to hospital. The two of our cases who had the more acute onset of symptoms (Cases 2 and 3) presented with an acute organic brain syndrome, characterized by confusion, disorientation, and hallucinations. Case 3 cleared mentally in two weeks, but Case 2 took three months to clear. Neither of these women have been tested psychologically, but we think that both have been left with a slight organic mental impairment. Two cases (Cases 1 and 2) had slow nerve conduction velocities to confirm the diagnosis of neuritis, and had EMG evidence of chronic lower motor neurone disease.

DISCUSSION

Bartholomew (1961) was the first to report that the

chronic use of glutethimide could cause nervous system impairment which lasted for some time after withdrawal of the drug. He briefly reported two cases with a mild peripheral neuritis in the legs that cleared up about 10 weeks and four months after withdrawal of the drug. Lingl (1966) was the next to report on the 'irreversible effects of glutethimide addiction'. His single case, who very much resembles our Case 2, took glutethimide for over 4½ years, finally reaching a regular daily dose of up to 5.5 g. In the course of several months the patient's gait deteriorated, and she was hospitalized for inability to walk and confusion. She showed the following neurological findings: 'mydriasis, slight horizontal nystagmus, scanned speech, diminished muscle tone in lower limbs, inability to stand unsupported due to severe ataxia of station, and pronounced ataxia of lower extremities and trunk. In the upper extremities the ataxia was less severe, but she was unable to write legibly'. Psychological testing indicated 'diffuse organic brain pathology with psychotic reaction'. Improvement occurred gradually. Eight months after admission, ataxia could still be demonstrated in upper and lower extremities, and there were persisting symptoms of an organic mental syndrome.

When thalidomide was on the market, various reports appeared which showed that it could cause a neuropathy (Fullerton and Kremer, 1961; Buckle, 1963). The neuropathies, either purely sensory or mixed motor and sensory, were mostly mild and slowly progressive, yet tended to fade slowly after withdrawal of the drug. Most of the affected patients had taken the recommended dose for night-time sedation. Almost none had a significant intake of alcohol. We believe our evidence shows that glutethimide, which is structurally similar to thalidomide (alpha-ethyl-alpha-phenylglutarimide as compared with alpha-phthalimidoglutarimide), can cause a neuropathy similar to that of thalidomide in that it is mild and has somewhat more prominent sensory than motor manifestations. However, glutethimide can cause striking and poorly reversible cerebellar symptoms, and long-lasting mental symptoms, neither of which were reported with thalidomide. Another difference between the two drugs is in the dose needed to produce nervous system damage: thalidomide gave damage in the usual doses taken regularly in the course of many months without concomitant alcohol intake or malnutrition; glutethimide has only produced damage when taken generally a year or more in larger daily amounts than the usual sedative dose and, in our cases, in association with drinking or poor nutrition. Thus glutethimide is a less potent

as well as a qualitatively different neurotoxic agent than thalidomide.

In the cases of thalidomide neuropathy, the thalidomide is clearly the causative agent because of the absence of complicating factors. The causative relation of the glutethimide to the neurological symptoms in our cases might be questioned because of the presence of complicating factors: drinking and poor nutrition. However, a close look at the evidence indicates that glutethimide was toxic to the nervous system. Most importantly, all cases took glutethimide in moderate to heavy amounts for a long time, and glutethimide, as we have mentioned, chemically resembles thalidomide, a known neurotoxin. The neurotoxic effects of alcohol—if such effects do indeed exist—can readily be eliminated as a necessary factor in our patients' disease, because Case 1 did not drink for five years and Case 3 stopped drinking a few weeks before the onset of symptoms. We cannot so easily eliminate nutritional deficiency as an important factor in the production of our patients' diseases, because Case 1 ate very poorly for many months before the onset and during the evolution of her symptoms; Case 3 had frequent nausea and some vomiting and no doubt ate poorly for at least a month before the onset of symptoms; and Case 2, though she probably ate well, could not document this with a decent history. Neither Lingl (1966) nor Bartholomew (1961) mentioned the nutritional states of their patients. If our cases suffered nervous system damage from malnutrition rather than from a toxic effect of glutethimide, we would expect their symptomatology to be that of a known nutritional disease. Only two nutritional diseases—Wernicke's encephalopathy, due largely or even entirely to thiamine deficiency and often associated with neuritis (Victor and Adams, 1961), and alcoholic cerebellar degeneration, probably related to malnutrition and often associated with neuritis (Victor, Adams, and Mancall, 1959)—bear any resemblance to our patients' illnesses. The resemblance, however, is insufficient for us to believe that any of our cases had either of these two clinical entities. For example, Wernicke's encephalopathy can be excluded by our patients' lack of the expected ocular findings of this disease. Also, two of our cases had gross upper limb ataxia, an almost unheard of finding in Wernicke's disease. Furthermore, two of

our cases, despite having marked and long-lasting mental changes, were left with no signs of Korsakoff's psychosis (Jolliffe, Wortis, and Fein, 1941; Victor and Adams, 1961). Alcoholic cerebellar degeneration is excluded by the gross upper limb ataxia in two cases (rare in alcoholic cerebellar degeneration), and by the considerable, albeit slow in two cases, recovery of gait in all three of our patients (the ataxia of alcoholic cerebellar degeneration remains much the same once it reaches its peak) (Victor *et al.*, 1959).

Thus, we believe that glutethimide was toxic to the nervous system in our three cases. Nutritional deficiency, especially thiamine deficiency, and even the intake of alcohol may well have been contributory factors. Perhaps glutethimide interferes with those biochemical pathways that are also hampered by a deficiency of thiamine. This thought is suggested by the work of Buckle (1963), who showed in cases of thalidomide neuropathy, elevated pyruvic acid blood levels, and abnormal pyruvic acid tolerance tests, and their return to normal after the administration of thiamine.

SUMMARY

Three cases of nervous system damage due to the heavy chronic ingestion of glutethimide are presented, and the four previously reported cases are reviewed. Glutethimide is shown to cause cerebellar ataxia, peripheral neuropathy, and organic mental changes.

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