L-DOPA AND BENSERAZIDE IN THE TREATMENT OF ACUTE HEPATIC ENCEPHALOPATHY IN INFANCY

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SYNOPSIS

Use of L-Dopa and Benserazide in a 5 month old infant with fulminant hepatic failure was associated with transient improvement in the level of consciousness and deterioration following withdrawal of the drug on two consecutive occasions. Electroencephalogram revealed significant improvement 24 hours after starting treatment. Although there is no conclusive evidence that it affects the eventual outcome, the use of 1-dopa may be considered in cases which do not respond to conventional treatment of hepatic coma.

INTRODUCTION

Acute hepatic encephalopathy is associated with a mortality ranging from 50% to 85% (Lunzer, 1975). Varying methods currently used in its treatment, reflect an inadequate understanding of the pathogenesis of this disorder. Accumulation of false neurotransmitters eg. octopamine and B-phenylethanolamine has been incriminated in the pathogenesis of the neurological changes (Fischer and Baldessarini, 1971). L-dopa has been reported useful in restoring the physiological neurotransmitters and in reversing the neurological derangements (Parkes et al, 1970, Fischer and James, 1972). Since then encouraging results have been reported by some (Datta et al, 1976; Chajek et al, 1977) but not all groups of workers (Lunzer et al, 1974).

This paper reports improvement in electroencephalographic tracings and level of consciousness following two separate administrations of L-dopa and benserazide (Madopar) therapy in an infant with hepatic encephalopathy secondary to acute fulminant hepatitis, not associated with HBs Ag.

CASE REPORT

A 5 month old female Chinese infant, treated at age 1 month in a private hospital for cow's milk protein intolerance and septicaemia and who had received a blood transfusion, was admitted to the University Hospital with a 5 day history of low grade fever and progressive jaundice, culminating in drowsiness, vacant stare and lack of response to the parents' overtures. The patient, the only child of a carpenter, was delivered normally and birth weight was 3.1 kg. She smilled at 3 months and had recently learned to roll over but was unable to sit unaided. On examination, weight was 6 kg, length 65 cm, head circumference 40.5 cm. She was severely jaundiced, drowsy and

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restless. Heart rate was 140 beats/minute and respiratory rate was 35/minute. Her abdomen was distended, the liver was enlarged 5 cm and the spleen 7 cm below the rib margin. The patient was unable to roll over, grasp an object or follow a bright light. The rest of the clinical examination was normal. A diagnosis of hepatic encephalopathy secondary to fulminant hepatitis was made and treatment was started with intravenous glucose-saline, rectal washout and oral neomycin 6 hourly. Investigations revealed haemoglobin 8.2 g/dl, total leukocyte count 15.3 x 10^{-9}/L, polymorphs 57%, lymphocytes 38%, monocytes 1%, basophils 2%, serum sodium 140 mmol/1, potassium 5.5 mmol/1, urea 1.66 mmol/1, serum total bilirubin 231 umol/1, SGOT 1240 IU/L SGPT 60 IU/L, alkaline phosphatase 570 IU/L, serum albumin 31 g/1, serum globulin 35 g/1 and HBsAg was negative. Over the next few days, the patient became more drowsy. The liver became unpalpable and the spleen size decreased to 1 cm. The results of investgations are recorded in Table I.

The patient was given 150 ml blood and started on daily vitamin K 5 mg intravenously and oral Madopar (Roche) 125 mg qid on 14.2.79. Within 24 hours, the infant became alert, was able to follow a bright object through 180° movement, responded and smiled to parents' overtures and was able to roll over partially. By 36 hours she was awake all the time, crying and irritable. Treatment was then stopped. The patient was reintroduced to a hypoallergenic milk formula (Nutramigen) which she tolerated well. She remained improved but gradually began to lose interest in her surroundings. A second course of Madopar was given on 28.2.79 with good results. The clinical features and results of biochemical and electroencephalographic studies before and after Madopar therapy, are recorded in Table I and figure 1. Madopar therapy was stopped on 1.3.79 because of the infant's restlessness and inability to sleep but by 6.3.79, the infant was again drowsy and unable to follow objects. She was taken home on leave to visit a temple and did not return.

Table I Clinical features and results of biochemical and electroencephalographic studies before and 24 hours after Madopar

	Before l-dopa (14.2.79)	24 hours post l-dopa (15.2.79)	Before l-dopa* (28.2.79)	24 hours post l-dopa@ (1.3.79)	Off l-dopa (6.3.79)
Clinical Features					
Consciousness	V. Drowsy	Alert	Drowsy	Awake, refuses to sleep	
Follow object 180°	No	Yes	±	Yes	No
Response to overtures	Poor	Good	Poor	Good	Fair
Roll over	No	Partial	No	Partial	No
Feeding	Fair	Good	Fair	Good	Fair
Biochemical Tests		(17.2.79)	(23.2.79)		
Serum total bilirubin (umol/l)	393	479	462	402	—
SGOT (IU/L)	26	23	46	70	—
SGPT (IU/L)	60	46	44	16	—
Serum alkaline phosphatase (IU/L)	400	78	200	216	—
Prothrombin time (%)	10	10	10	15	—
Blood ammonia (normal 0-70 ug/dl)	261.5	169.5	—	10.5	—

Electroencephalogram

*Before Madopar	24 hours after Madopar@
Background of predominantly diffuse irregular delta waves at 1½-3 c/s seen symmetrically over both sides. Some rhythmic delta waves of moderately high voltage at 1½ c/s seen over anterior regions of both sides. Low voltage beta waves at 18 c/s seen on both sides. Very scanty theta waves at 4-6 c/s seen.	Background of 3-4 c/s wave forms mainly over both temporal areas especially the left. 5-6 c/s theta wave forms seen over both occipital areas. Beta rhythm at 22 c/s seen symmetrically over both occipital and temporal head regions. Photic driving is irregularly seen over both sides.
Impression: Moderately abnormal.	Impression: Improved — mildly abnormal.

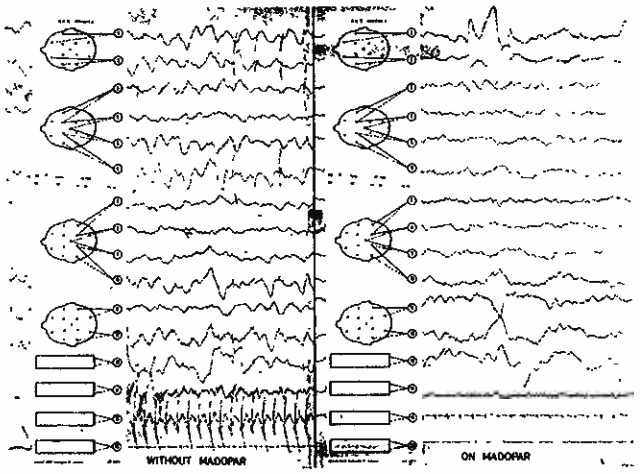

Figure 1. Electroencephalagraphic tracings before and 24 hours after Madopar therapy.

DISCUSSION

The exact mechanism of action of L-dopa in hepatic coma is not known but it has been suggested that false neurotransmitters eg. octopamine, produced in the intestine from degradation of nitrogenous substances and normally detoxified in the liver, reach the cerebral circulation unchanged in cases of acute or chronic liver disease via porto-systemic collaterals. These false neurotransmitters compete with dopamine, a synaptic neurotransmitter in the reticular formation of the brain stem and cause unconsciousness by competitive blockage. L-dopa, a precursor of dopamine is able to replace the false neurotransmitter after conversion to dopamine and thus improve consciousness (Datta et al, 1976; Chajek et al, 1977).

Although there is no definite evidence the drug is of value in patients with encephalopathy and underlying cirrhosis, there is reason to feel that l-dopa may be more useful in acute hepatic failure than in chronic encephalopathy as seen in our case. It can be argued that the transient changes in our patient's level of consciousness and in the EEG may be due to fluctuations in the severity of hepatic encephalopathy, which are not unusual in some patients. Improvement in consciousness within 24 hours on 2 consecutive occasions following administration of l-dopa and deterioration following its withdrawal together with the EEG changes suggest more than a coincidental relationship. A progressive fall in blood ammonium level was observed in our patient over a period of 3 weeks which does not seem to have a strict correlation either with the patients neurological status or the results of the other liver function tests. Blood ammonium may be normal in patients with hepatic coma (Phear et al, 1955) and is probably a better indicator of portal-systemic shunting which occurs in liver disease than of hepatocellular function per se (Sinniah, 1967). Oesophageal varices can appear and disappear spontaneously within short intervals of time (Palmer, 1957) and account for the apparently contradictory results. L-dopa does not improve hepatic function but improved consciousness would help a patient adjust better to illness than an unconscious state. We have used Madopar which comprises L-dopa and benserazide, a carboxylase inhibitor which helps delay the breakdown of dopamine and maintain higher effective levels of the drug. Our experience with the index case suggests that L-dopa can be used in infancy and may produce remarkable improvement in consciousness. We feel its use would be justified in cases of hepatic coma where other measures fail.

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