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Levodopa in Hepatic Coma in Children*

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L-dopa was first used by Parkes and co-workers[1] orally for the treatment of three patients with acute hepatic failure, resulting in temporary improvement. Since then 33 cases treated with levodopa were reported, almost all in adult literature[2-10] only two being in the pediatric age[2,7] group. Since we have treated 40 children with hepatic encephalopathy with this drug, in the 45 months since February 1971, we thought it would be worth publishing our retrospective results. L-dopa could not be obtained for treatment of 20 patients with hepatic coma and these served as controls.

Materials and Methods

The ages of the patients in the L-dopa treated group ranged from five months to sixteen years, with mean of 6.9 years; 28 were males and 12 females. In the control group the mean age was 9.3 years with the range of 18 months to 16 years; 6 were girls and 14 were boys.

All 60 patients were investigated for precipitating factors of liver failure by history, X-ray and laboratory methods and were divided into two general groups, 22 cirrhotics and 38 hepatitis patients. These diagnoses were clinical but could be verified by tissue examination in 17 of the 22 cirrhotics, (12 of 15 from the study group and 5 of from the control group). Tissue diagnosis could also be made in 20 patients and 5 of 13 from the control group, in pre-and/or postmortem examinations.

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The patients in both groups were in stages of III to V coma on admission, according to Plum and Posner's[11] clinical criteria. Liver function tests including SGOT, SGPT, serum bilirubin, total proteins (albumin globulin), alkaline phosphatase, thymol turbidity, plasma ammonia level and cephalin cholesterol floculation tests were carried out. In addition, prothrombin time (PT), partial thromboplastin time (PTT) were carried out according to Quick[12] and Rodman, et al,[13] respectively. Percutaneous liver biopsies were performed with the Vim-Silverman's needle.

L-dopa was given by naso-gastric tube and the dose ranged from 600 mg to 5 gm, according to the weight (about 100 mg/kg). It was given more than once in 4 of the patients, the most being 4 times to one patient. Oral neomycin was started for all patients; plasma, albumin, blood transfusions and parenteral antibiotics were used according to the patients' requirements. Intravenous corticosteroid (solu-cortef 2 mg/kg) was given randomly and exchange transfusions were attempted when fresh blood (at least 100 ml/kg) was available.

Results

Cirrhotics: There were 22 patients in this group; L-dopa could not be given to 7 of them who served as controls. One of the cirrhotics in the study group was discharged contrary to medical advice, just after L-dopa administration. With the exception of this case, of the 14 patients treated with levodopa, 11 improved clinically within 12 hours and 8 of these were discharged from the hospital. Three of the 14 were also given corticosteroid (in two, prior to L-dopa), and two had exchange transfusions (one before L-dopa). Of nine patients treated with levodopa only 7 improved and 6 could be discharged (Table I). None of the 7 cirrhotics in the control group regained consciousness, dying within a few days. One of these was given corticosteroid (I.V.) and none had exchange transfusion.

Hepatitis patients: This group was composed of 13 control and 25 study cases. In the control group four of the 13 patients with hepatitis could be discharged from the hospital. Five of these 13 patients were exchanged 1 to 3 times; only one improved and was discharged from the hospital. None of the 6 patients who were given corticosteroid (1. V.), 3 of whom were also exchanged, showed improvement and subsequently died. Among the L-dopa treated hepatitis patients, 12 showed some improvement clinically within 12 hours and 9 of these could be discharged; the rest died. Exchange transfusions were carried out in 9 of the

TABLE I

THE RESULTS OF L-DOPA TREATMENT COMPARED TO THE RESULTS OF SUPPORTIVE TREATMENT ONLY

Hepatic Coma	Treated without L-dopa					Treated with L-dopa				
	No. of Cases	CS*	ET**	Improved	Discharged	No. of Cases	CS*	ET**	Improved	Discharged
Due to cirrhosis	7 (6) +	1	0	0	0	14 (9) +	2	2	11 (7) +	8 (2 had CS*) (6) + (1 had ET**)
Due to hepatitis	13 (5) +	6	5	4 (3) +	4 (1 had ET**) (3) +	25 (14) +	6	9	12 (8) +	9 (2 had ET**) (7) +
Total	20 (11) +	7	5	4 (3) +	4 (3) +	39 (23) +	9	11	23 (15) +	17 (13) +

CS* = Corticosteroid

ET** = Exchange transfusion

·|- = Patients who did not receive either glucocorticoid or exchange transfusion.

TABLE II

THE LIVER FUNCTION TESTS OF L-DOPA RESPONSIVE PATIENTS, COMPARED TO THOSE WHO SHOWED NO IMPROVEMENT (BEFORE L-DOPA TREATMENT)

	SGOT (ku)	SGPT (ku)	Ammonia (mcg %)	P. T. (sec)	PTT (sec)	Bilirubin (mg %)
Responsive	(23) *	(23) *	(17) *	(20) *	(16) *	(22) *
mean & S.D.	419.9±445.9	300.4±445.9	200.5±81.9	53.5±67.3	183.4±60.5	11.9±8.4
S.E.	116.9	93.1	19.9	15.0	15.1	1.8
range	(18–1400)	(6–1400)	(100–420)	(15–240)	(77–300)	(0.8–38)
Nonresponsive						
mean & S.D.	664.3±623.2	565.0±498.1	204.9±73.8	93.8±81.6	233.8±81.6	23.4±10.3
S.E.	155.8	124.5	27.9	23.6	19.9	2.7
range	(50–2000)	(25–1400)	(144–364)	(23–300)	(142–300)	(10.5–49.6)
P	0.05	0.05	0.05	0.05	0.05	0.001

* = Numbers in parentheses indicate the number of patients in whom test could be carried out.

TABLE III

THE COMPARISON OF LIVER FUNCTION TESTS BEFORE AND AFTER L-DOPA TREATMENT IN PATIENTS WHO RESPONDED WELL TO THIS TREATMENT

	SGOT (ku)	SGPT (ku)	Ammonia (mcg/100 ml)	P. T. (sec)	PTT (sec)	Bilirubin (mg %)
Before	(23) *	(23) *	(17) *	(20) *	(16) *	(22) *
mean & S.D.	419.9±559.9	300.4±445.9	200.5±81.9	53.5±67.3	183.±60.5	11.9±8.4
S.E.	116.9	93.1	19.9	15.0	15.1	1.8
range	(18–1400)	(6–1400)	(100–420)	(15–240)	(77–300)	(0.8–38)
After	(14) *	(14) *	(17) *	(5) *	(3) *	(14) *
mean & S.D.	231.4±128.5	137.7±103.3	127.7±89.2	33.2±7.5	187	14.3±8.84
S.E.	34.3	27.6	21.6	3.4		2.4
range	(71–480)	(10–340)	(60–420)	(26–46)	(160–219)	3.3–28)
P	0.05	0.05	0.05	0.05	not compared	0.05

* = Numbers in parentheses indicate the number of patients in whom tests could be carried out.

patients with hepatitis; only 2 improved and lived, but in both cases levodopa was used following exchange transfusion. The 7 remaining patients were given L-dopa prior to exchange transfusion, but all failed to respond and later died. Corticosteroid was used in 6 patients (in 3 prior to L-dopa administration); 4 also had exchange transfusions, but none showed any improvement and died.

Thirteen of twenty-three of the patients (56.5 %) treated with levodopa who did not receive either glucocorticoid or exchange transfusion, could be discharged. Only 3 of the 11 control patients (27.2 %) with similar selection could also be discharged ($p < 0.04$). 23 of the 39 patients in this study (59 %) treated with L-dopa showed some clinical improvement and 17 of these (44.7 %) could be discharged from the hospital. This was more than 100 percent better than the control group in which survival was 20 % (Table I).

SGOT, SGPT, ammonia, serum bilirubin, PT and PTT initial values of the improved patients were compared with the initial values of the patients who died in the hospital (including those who showed immediate improvement and those who showed no improvement), following L-dopa treatment. With the exception of bilirubin values, no statistically significant differences were seen in the comparison of the other values (Table II). In the L-dopa treated group some of the liver function tests on admission were compared with the values following clinical improvements, but statistically significant improvement could not be shown (Table III).

Discussion

Liver cirrhosis and consequential liver failure is not infrequently seen among children in Turkey. The prevalence of HBsAg is also high (3.2 %) in the Turkish population[15] and hepatic coma due to hepatitis is rather frequent. In liver failure, our supportive treatment, which consists of elimination of precipitating factors, control of gastro-intestinal (GI) bleeding, decreasing GI bacteria by neomycin, treatment of infections, correction of hyponatremia and hypokalemia, I. V. glucose, plasma and/or albumin administration[16] was applied for all patients. In addition, sixteen of the patients (including 11 of the L-dopa treated cases) had had exchange transfusions, but only 4 of these (25 %) lived. Although the collected data from literature might suggest some beneficial effects of exchange transfusions on hepatic coma in children, which were mostly due to acute hepatitis,[17] our results did not support this; however they were comparable to the results of adult cases.[18] Intra-

venous corticosteroid did not seem to be of any help in the treatment of these patients either. Altogether, 16 cases were given corticosteroid and only 2 of these (12.5 %) improved and lived. However, with oral administration of L-dopa there was a marked improvement in the patients' consciousness within a short period in 2/3 of the cases and almost half of these could be discharged from the hospital. It should be added that 7 of the patients (17.9 %) treated with L-dopa, died within 12 hours of administration of the drug, which was not long enough for the effect of the drug to be seen. It has also to be emphasized that in spite of marked improvement, especially in the patients with cirrhosis, the basic disorder could not be influenced.

It seems that some factors, other than the degree of liver disturbances determine the immediate prognosis of L-dopa treated patients; as is seen in Table II, with the exception of total bilirubin values, other liver functions tests were not significantly different between L-dopa responsive and unresponsive patients. Although GI intolerance to L-dopa has been reported we could not evaluate it since all these patients had had GI-symptoms prior to administration of the drug.[8] We evaluated unconjugated bilirubin levels prior to and after L-dopa administration in 15 cases. Although it was our impression that unconjugated bilirubin levels elevated after L-dopa as started previously,[8] statistical evaluation did not support this impression ($p > 0.05$). (Table III). The evaluation of hepatitis patients together with cirrhotics seems to be reasonable. Since L-dopa was effective in the arousal of the patients with hepatic encephalopathy without influencing their liver functions.

In evaluation of the patients, EEG studies were not possible because of the difficulties of moving patients in such serious condition to the laboratory. Also in our opinion, improvements shown by EEG studies would not be sound criteria for the prognosis; our evaluation was based on the clinical condition which allowed the patients' discharge.

The nature and site of metabolic disorders responsible for hepatic coma is not known. However, at the present time the acceptable hypothesis is, failure of the liver to detoxify nitrogenous substances of intestinal origin and metabolize blood ammonia, together with changes in acid base balance and in cerebral blood flow and cerebral neurochemical transmission in the synapsis of reticular formation. The studies of Fischer and James of urine of patients with hepatic coma and animal experiments, strongly suggest that an increased amount of false neurochemical transmitters are present in the general circulation of patients with hepatic coma and in the brain tissues of animals with liver failure. The evaluation

of S-adenosyl methionine level in the brain and methionine in the blood during liver failure as demonstrated previously[19] supports Fischer and James studies.[6, 20]

L-dopa is a precursor of dopamine which is mainly confined in the C. N. S. to the substantia nigra, striatum and caudata nucleus.[21] When L-dopa is given in hepatic coma, it enters easily into tissues and increases the dopamine concentration.[1, 6] Certain neurological manifestations occasionally seen in chronic hepatic encephalopathy, namely rigidity, tremor and akinesia are common in Parkinson's disease, in which dopamine depletion of the substantia nigra and striatum has been proved.[21, 22] It has also been shown that L-dopa considerably decreases the S-adenosyl methionine concentration (which is elevated during liver failure[19]) in the brain by combining with it. Thus, levodopa by decreasing the S-adenosyl methinonine level may depress the production of some false neurochemical transmitters such as phenylethanolamine, and by increasing the dopamine level in the substanti nigra, striatum and especially in reticularis, would be effective on the deranged brain functions in hepatic coma. As reported previously no immediate improvement could be shown in liver function tests (SGOT, SGPT, blood ammonia, P. T. and bilirubin values) in the patients who responded to levodopa (Table III). These findings may support the above hypothesis that hepatic coma is a cerebral neurotransmitter disorder and could be treated transiently without influencing liver functions.

Whatever the final explanation for the effect of L-dopa is, we can say that it heals the patients in hepatic coma considerably. In our opinion L-dopa treatment should be tried in all patients with hepatic encephalopathy. Very recently it has been used intravenously in at least four cases, without reportable complications. By this route we are hopeful of obtaining better results, since it is not always possible to administer the drug orally in some of these cases, due to vomiting or gastro-intestinal disturbances.

These several different treatments were attempted in these patients, since the hepatic coma (encephalopathy) presents such a grave and desperate situation.

Summary

Levodopa was used orally (approximately 100 mg/kg) for the treatment of hepatic encephalopathy in 40 children, aged five months to 16 years. 15 of these patients had cirrhosis of the liver and 25 had hepatitis. The diagnosis was verified in 12 and 15 patients, respectively. L-dopa was

combined with supportive treatment in each case. By the addition of levodopa to the treatment 44.7 % of the patients could be discharged from the hospital, compared with 4 of 20 patients (20 %) who were given the same supportive treatment, but no levodopa. Corticosteroid (I. V.) did not seem to be at all effective (which was administered to 16 cases in all). Exchange transfusion was used in the treatment of 17 cases of hepatic coma but was not found effective either.

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