A sequential trial of tolbutamide in hypoproteinaemia in adults

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EDITORIAL SYNOPSIS Tolbutamide, 1.0 g. daily, has been shown to cause clinical improvement in patients with malnutrition and was associated with an increase in plasma proteins.

A definite increase in the glycogen content of the liver with tolbutamide administration in animal experiments has prompted some workers to investigate the action of the drug on liver diseases in man. Such an idea was based on the assumption that augmenting glycogen in the liver must have a beneficial effect on the damaged liver. Knick and Emrich (1957) used tolbutamide, 3 g. daily for three to six weeks, in six cases of chronic hepatitis and six cases of liver cirrhosis without diabetes and reported increased appetite, decrease in serum bilirubin, marked restoration to normal of the serum proteins, and improvement in the bromsulphalein test. Improvement in bromsulphalein excretion was also reported in a diabetic patient by Pote, Anderson, and Cochran (1959). László, Bruckner, Görgey, and Tóth (1959) treated 50 patients suffering from acute hepatitis and found that decrease in serum bilirubin and recovery time were both hastened by tolbutamide when compared with a similar group of controls. In liver biopsy studies Dobrzański (1959) noted excess of glycogen in liver cells, diminution of vacuolization of liver cell nuclei, and distinct regression of fatty changes in the liver in 12 tolbutamide-treated diabetic patients.

Singh, Sehra, and Bhargava (1961) treated 55 cases of cirrhosis of the liver suffering from anorexia, emaciation, anaemia, hypoproteinaemia, and gross ascites with tolbutamide and reported improvement in appetite in 45 cases (82%), control of ascites in 42 cases (76%), weight gain in 36 cases (66%), increase in serum proteins in 35 cases (64%), and improvement in the haemogram in 24 cases (44%). Liver-function tests showed moderate improvement in 26 cases (47%) but there was no deterioration in the remaining 29 cases. Bhattacharyya and Mandal (1963) reported comparable results in 10 cases of cirrhosis of the liver from the Calcutta School of Tropical Medicine. Under tolbutamide therapy

total serum proteins improved progressively in seven cases, there was initial improvement followed by deterioration in two cases, and practically no change in one case. Rapid improvement in the albumin fraction was a striking feature when the initial serum albumin level was below 2 g. %.

It was felt by us that the increase in serum proteins under tolbutamide administration may not necessarily be confined to diseased livers. Thus, pre-treatment of rats with tolbutamide had been observed to increase the incorporation of ^{14}C -glycine into protein in liver slices by Recant and Fischer (1957); and DeMeutter, Khachadurian, and Marble (1958) had noticed that tolbutamide injected intravenously into human subjects decreased serum α -amino-acids. We were, therefore, prompted to try the effect of tolbutamide in the treatment of hypoproteinaemia from any cause. Using the restricted closed design sequential trial technique, advocated by Armitage (1960), we have found the results to be satisfying in malnutrition and malabsorption; previous reports of increase in serum proteins with tolbutamide in cirrhosis of the liver (*vide supra*) have been confirmed.

MATERIAL AND METHOD

The patients were 40 Indians, 28 men and 12 women, 24 to 60 years old. They were admitted to hospital for debility, oedema, and hypoproteinaemia.

An initial estimate of the clinical status of each patient (*vide infra*) was made and the cause of his hypoproteinaemia was determined. Those resulting from malnutrition, malabsorption, and cirrhosis of the liver were selected for the trial; cases with malignant disease and tuberculosis of the bowel were not included.

During the period of investigation of the cause of hypoproteinaemia the opportunity was taken to accustom the patients to their environment. When the investigations permitted they were given the standard high-protein

hospital diet and tablet B (placebo) twice daily before food.

These investigations were completed in two weeks and the patients were then ready for the tolbutamide trial. A pre-treatment estimate of the clinical status of each patient, comprising his sense of well-being, state of oedema, weight, and the serum proteins, total as well as albumin and globulin, was made. The patients were weighed to the nearest 0.05 kg. and the proteins were estimated by the biuret method as described by Harrison (1957). The trial, which was double blind, then commenced. All comparable cases were paired by randomization. In each pair one patient received tablet A (tolbutamide) and the other tablet B (placebo) twice daily before food. The dose of tolbutamide was 1.0 g. daily. All patients continued to remain on the standard high-protein hospital diet to which they had been introduced earlier. The therapy was continued for four weeks and the post-treatment estimate of the clinical status and of the serum proteins was made in each case on its termination.

Results were assessed by sequential analysis. The criteria for assessment, whether in each group therapy A or B was better of the two, were (1) subjective improvement, (2) weight gain, (3) reduction in oedema, and (4) improvement in serum protein levels. One treatment was regarded as being superior to the other which was superior with at least three out of the four assessments. The pairs were thus designated AB (A better than B), BA (B better than A), or T (tied pair in which a distinction could not be made between the two drugs).

A restricted closed design was chosen for the experiment. Before the trial began it was estimated that a placebo was unlikely to produce noticeable improvement, as judged by the criteria, in more than 15% of the cases. If tolbutamide raised this by 50%, i.e., to 65%, then it could be claimed that the difference was sufficiently great in favour of the drug. From this combination, $\pi_1 = 0.65$ and $\pi_2 = 0.15$, the value of $\theta_1 = 0.913$ (approximately 0.9) was obtained (Table 4.1 of Armitage, 1960). The boundaries were drawn with $\theta_1 = 0.9$, $2\alpha = 0.05$, and $1 - \beta = 0.95$ (Table 3.7 of Armitage, 1960).

RESULTS

Table I gives the experimental data. The causes of hypoproteinaemia were malnutrition (12 cases), malabsorption (20 cases), and cirrhosis of the liver (eight cases). The pre-treatment protein levels varied from 2.2 to 4.8 g. %. Forty patients (20 pairs) entered the trial. On the basis of criteria for assessment, two pairs were tied and 18 pairs were untied, 15 pairs for tolbutamide and three pairs for placebo.

Figure 1 shows the experiment. The sample path is drawn with the number of pairs against the excess preferences. The experiment was concluded at the eighteenth pair when the upper boundary was crossed by the path and a significant advantage for tolbutamide therapy was established.

DISCUSSION

In Table I and Fig. 1 there is a definite advantage to group A (tolbutamide therapy). The value of the treatment has been enhanced by collation of evidence from all four criteria of assessment, i.e., subjective improvement, weight gain, reduction of oedema, and improvement in serum protein levels into a single judgment whether tolbutamide was a success against placebo controls or not, and by limiting the duration of the trial to four weeks. Thus, discrepancies in assessment of results due to chance, inaccuracy in protein estimations, or loss of objectivity of any single parameter have been avoided. Table II gives details about the changes which took place in each patient between admission to the hospital and entry to the trial. There is no indication in Table II that, by at least three criteria of assessment, group A cases were by any chance doing better before the treatment started. The rises noted in serum proteins in some group A or group B cases are too insignificant for consideration.

We are not sure about the exact mode of action of tolbutamide in these cases. It appears, however, that the beneficial effect may accrue from (1) insulin release, (2) increased sodium excretion, and (3) improved digestion.

FIG. 1. Treatment with tolbutamide versus placebo. Restricted closed design with $2\alpha = 0.05$, $1 - \beta = 0.95$, $\theta = 0.90$, and $N = 19$.

TABLE I

EXPERIMENTAL DATA (AFTER TREATMENT)

Pair No. and Treatment Group	Age	Sex	Cause of Hypoproteinaemia	Subjective Improvement ¹	Loss of Oedema ²	Weight (kg.)		Weight Gain: Difference in Favour of A or B (kg.) ³	Total Proteins (g%)		Improvement in Serum Proteins: Difference in Favour of A or B (g.%)	Advantages to A or B as Judged by the Criteria	Types of Pair	
						Before Therapy	After Therapy		Before Therapy	After Therapy				
1	A	38	M	Protein malnutrition	Good	++	62.85	64.30	0.40 A	3.8	4.8	0.8 A	A	AB
	B	42	M	Protein malnutrition	Poor	—	68.45	69.50		2.8	3.0			
2	A	58	M	Malabsorption syndrome	Good	+++	56.50	58.00	0.35 A	3.6	4.2	0.6 A	A	AB
	B	50	M	Malabsorption syndrome	Poor	+	60.10	61.25		3.8	3.8			
3	A	48	F	Malabsorption syndrome	Moderate	++	58.85	60.35	0.55 B	3.4	4.0	0.4 B	B	BA
	B	40	F	Malabsorption syndrome	Moderate	++	54.60	56.65		3.2	4.2			
4	A	60	F	Malnutrition	Moderate	++	60.45	62.30	0.55 A	4.0	5.4	1.0	A	AB
	B	48	F	Malnutrition	Poor	—	55.05	56.35		3.8	4.2			
5	A	42	M	Malabsorption	Good	+++	64.25	65.85	0.40 A	4.0	5.8	1.5 A	A	AB
	B	38	M	Malabsorption	Poor	—	71.25	72.45		4.1	4.4			
6	A	50	M	Cirrhosis of liver	Moderate	++	59.90	60.10	0.25 A	3.0	4.6	1.8 A	A	AB
	B	46	M	Cirrhosis of liver	Poor	—	55.90	55.85		3.2	3.0			
7	A	45	M	Malnutrition	Good	+++	67.20	69.35	0.65 A	3.6	5.4	1.4 A	A	AB
	B	38	M	Malnutrition	Moderate	+	63.35	64.85		2.8	3.2			
8	A	43	F	Chronic diarrhoea	Good	++	58.40	60.40	0.65 A	4.0	6.0	1.8 A	A	AB
	B	48	F	Chronic diarrhoea	Poor	—	51.85	53.20		3.6	3.8			
9	A	52	M	Post-dysenteric syndrome	Good	++	65.60	66.80	0.45 A	3.2	6.4	2.4 A	A	AB
	B	58	M	Chronic diarrhoea	Moderate	+	68.70	69.45		2.8	3.6			
10	A	38	F	Malabsorption	Moderate	+	52.60	52.55	0.35 B	3.2	3.4	1.6 B	B	BA
	B	34	F	Malabsorption	Good	++	56.35	56.65		3.0	4.8			
11	A	54	M	Malnutrition	Poor	++	58.65	58.75	0.10 A	2.8	3.4	0.1 A	No advantage to either	T
	B	60	M	Malnutrition	Moderate	++	64.40	64.40		3.0	3.5			
12	A	56	M	Cirrhosis of liver	Poor	+	64.30	64.45	0.35 B	4.8	5.0	1.0 B	B	BA
	B	50	M	Cirrhosis of liver	Moderate	++	60.25	60.75		4.6	5.8			
13	A	28	F	Malnutrition	Moderate	+	42.45	43.65	0.40 A	4.4	5.4	0.6 A	A	AB
	B	24	F	Malnutrition	Poor	—	45.30	46.10		4.2	4.6			
14	A	50	M	Cirrhosis of liver	Good	++	68.25	69.45	0.60 A	4.0	5.0	0.7 A	A	AB
	B	40	M	Cirrhosis of liver	Poor	—	73.40	74.00		3.8	4.1			
15	A	48	M	Malabsorption	Good	++	51.15	52.45	0.55 A	3.8	4.6	0.6 A	A	AB
	B	43	M	Malabsorption	Moderate	—	58.30	59.05		3.6	3.8			
16	A	57	M	Malabsorption	Moderate	+	65.30	65.35	0.10 B	4.0	4.2	0.2 A	No advantage to either	T
	B	49	M	Malabsorption	Moderate	++	70.70	70.85		3.8	3.8			
17	A	40	M	Malabsorption	Good	++	72.55	73.85	0.40 A	4.2	5.4	0.6 A	A	AB
	B	46	M	Malabsorption	Poor	—	64.75	65.65		4.0	4.6			
18	A	42	F	Cirrhosis of liver	Good	+++	58.20	59.35	0.50 A	3.2	5.0	1.2 A	A	AB
	B	43	M	Cirrhosis of liver	Poor	—	54.85	55.50		3.0	3.6			
19	A	24	M	Malnutrition	Moderate	++	50.25	51.00	0.40 A	4.2	5.4	1.4 A	A	AB
	B	36	M	Malnutrition	Poor	—	52.65	53.00		3.8	3.6			
20	A	40	M	Malabsorption	Good	++	56.05	57.30	0.30 A	2.2	3.6	0.6 A	A	AB
	B	48	F	Malabsorption	Poor	—	54.25	55.20		2.8	3.6			

¹Subjective improvement was arbitrarily classified as good, moderate, and poor.²Likewise loss of oedema was classified as +++ (good response), ++ (moderate loss of oedema), + (slight loss) and — (no loss).³The actual weight gain in favour of any treatment was greater as weight of oedema fluid loss has not been accounted for.

TABLE II
EXPERIMENTAL DATA (BEFORE TREATMENT)

Pair No. and Treatment Group	Age	Sex	Cause of Hypoproteinaemia	Subjective Improvement ¹	Loss of Oedema ²	Weight (kg.)		Weight Gain: Difference in Favour of A or B (kg.)	Total Proteins (g. %)		Improvement in Serum Proteins: Difference in Favour of A or B (g. %)	Advantages to A or B as Judged by Criteria	Types of Pair
						On Admission	Before Therapy		On Admission	Before Therapy			
1	A	38	M	Protein malnutrition	Nil	62.95	62.85	0.20 B	3.8	3.8	0.2 B	To none	T
	B	42	M	Protein malnutrition	Nil	68.35	68.45		2.6	2.8			
2	A	58	M	Malabsorption syndrome	Nil	56.50	56.50	0.10 B	3.6	3.6	Nil	To none	T
	B	50	M	Malabsorption syndrome	Nil	60.00	60.10		3.8	3.8			
3	A	48	F	Malabsorption syndrome	Nil	59.00	58.85	0.30 B	3.4	3.4	0.1 A	To none	T
	B	40	F	Malabsorption syndrome	Nil	54.45	54.60		3.3	3.2			
4	A	60	F	Malnutrition	Nil	60.30	60.45	0.10 A	3.8	4.0	0.1 B	To none	T
	B	48	F	Malnutrition	Nil	55.00	55.05		3.5	3.8			
5	A	50	M	Malabsorption	Nil	64.15	64.25	0.05 B	4.1	4.0	0.3 B	To none	T
	B	38	M	Malabsorption	Nil	71.10	71.25		3.9	4.1			
6	A	50	M	Cirrhosis of liver	Nil	60.00	59.90	0.10 A	2.9	3.0	Nil	To none	T
	B	46	M	Cirrhosis of liver	Nil	56.10	55.90		3.1	3.2			
7	A	45	M	Malnutrition	Nil	67.20	67.20	0.20 B	3.6	3.6	0.1 B	To none	T
	B	38	M	Malnutrition	Nil	63.15	63.35		2.7	2.8			
8	A	43	F	Chronic diarrhoea	Nil	58.20	58.40	Nil	3.6	4.0	0.2 A	To none	T
	B	48	F	Chronic diarrhoea	Nil	51.65	51.85		3.4	3.6			
9	A	52	M	Post-dysenteric syndrome	Nil	65.80	65.60	0.30 B	2.8	3.2	Nil	To none	T
	B	58	M	Chronic diarrhoea	Nil	68.60	68.70		2.4	2.8			
10	A	38	F	Malabsorption	Nil	52.60	52.60	0.05 A	3.0	3.2	0.2 A	To none	T
	B	34	F	Malabsorption	Nil	56.40	56.35		3.0	3.0			
11	A	54	M	Malnutrition	Nil	58.50	58.65	0.10 A	2.8	2.8	Nil	To none	T
	B	60	M	Malnutrition	Nil	64.35	64.40		3.0	3.0			
12	A	56	M	Cirrhosis of liver	Nil	64.25	64.30	0.05 B	4.6	4.8	0.1 A	To none	T
	B	50	M	Cirrhosis of liver	Nil	60.15	60.25		4.5	4.6			
13	A	28	F	Malnutrition	Nil	42.25	42.45	0.10 B	4.3	4.4	0.1 B	To none	T
	B	24	F	Malnutrition	Nil	45.00	45.30		4.0	4.2			
14	A	50	M	Cirrhosis of liver	Nil	68.05	68.25	Nil	3.8	4.0	0.1 B	To none	T
	B	40	M	Cirrhosis of liver	Nil	73.20	73.40		3.5	3.8			
15	A	48	M	Malabsorption	Nil	50.85	51.15	0.05 A	3.7	3.8	0.1 A	To none	T
	B	43	M	Malabsorption	Nil	58.05	58.30		3.6	3.6			
16	A	57	M	Malabsorption	Nil	65.20	65.30	0.05 B	3.8	4.0	0.2 A	To none	T
	B	49	M	Malabsorption	Nil	70.55	70.70		3.8	3.8			
17	A	40	M	Malabsorption	Nil	72.35	72.55	0.05 B	4.0	4.2	Nil	To none	T
	B	46	M	Malabsorption	Nil	64.50	64.75		3.8	4.0			
18	A	42	F	Cirrhosis of liver	Nil	58.05	58.20	0.15 A	3.0	3.2	0.1 B	To none	T
	B	43	M	Cirrhosis of liver	Nil	54.85	54.85		2.7	3.0			
19	A	24	M	Malnutrition	Nil	50.00	50.25	0.10 A	4.0	4.2	0.1 A	To none	T
	B	36	M	Malnutrition	Nil	52.50	52.65		3.7	3.8			
20	A	40	M	Malabsorption	Nil	56.00	56.05	0.05 A	2.3	2.2	0.2 B	To none	T
	B	48	F	Malabsorption	Nil	54.25	54.25		2.7	2.8			

¹Could not be assessed as good, moderate, or poor.²Could not be assessed by clinical examination. The slight alteration in weight of patients was probably the result of minor changes in oedema.

EFFECT OF INSULIN RELEASE Insulin plays an important role in the metabolism of amino-acids and protein synthesis. The plasma level of amino-acids is elevated in patients with diabetic acidosis (Luetscher, 1942). Given to normal animals (Luck and Morse, 1933) and human subjects insulin causes a fall in the blood amino-acids. Frame and Russell (1946) noted that the administration of insulin in eviscerated rats depresses the rate of increase of plasma amino nitrogen that consistently follows this operative procedure. Insulin appears to enhance the rate of penetration of amino-acids across the cell membrane, as it does the penetration of glucose, and increases protein synthesis. Krahl (1953) reported the incorporation of ^{14}C -glycine into glutathione and into protein, which is greatly reduced in diabetes and is restored to normal by insulin, in liver slices. Sinex, MacMullen, and Hastings (1952), Krahl (1953), and Manchester and Young (1958) provided proof of augmentation by insulin of the incorporation of amino-acids into the protein of isolated rat diaphragm.

Pretreatment of rats with tolbutamide also increases the incorporation of ^{14}C -glycine into protein in liver slices (Recant and Fischer, 1957) and when injected intravenously in human subjects decreases the serum α -amino-acids (DeMeutter *et al.*, 1958). It is well established that the hypoglycaemic effect of tolbutamide is mediated by a release of increased amounts of insulin from the pancreas. Since the above effects of tolbutamide are identical with those of insulin, it would appear reasonable to assume that the increase in serum proteins obtained with tolbutamide has been obtained indirectly through release of insulin by it. Probably, however, tolbutamide, in addition to what it may indirectly promote through insulin secretion, has a direct effect of its own on protein synthesis. This is indicated in animal experiments, since Mohnike, Ulrich, Bibergeil, and Czyzyk (1957) noted that after tolbutamide in pancreatectomized and alloxanized dogs, without simultaneous blood sugar lowering, the level of amino nitrogen was decreased.

One of the outstanding effects of tolbutamide therapy is weight gain. This may be yet another indirect effect through release of insulin. The anabolic effect of insulin in the absence of somatotropin is now well-established (Salter, Davidson, and Best, 1956). However, tolbutamide appears to have a protein-sparing effect of its own. Bornstein (1957) found that tolbutamide decreased gluconeogenesis from protein by inhibiting the alanine transaminase. These observations were made *in vitro*, and were therefore independent of insulin.

INCREASED SODIUM EXCRETION Tolbutamide, as

shown by Mohnike *et al.* (1957), increases urinary output. The sodium excretion is also increased, as much as 40%, both in patients who have been previously on insulin treatment and in those who have been not on it. This effect is, therefore, shared only by tolbutamide and may play its own part in reducing the oedema.

IMPROVED DIGESTION With tolbutamide appetite increases before the end of a week. This is probably the result of increased gastric secretion and peptic output (Weiss and Sciales, 1961) and bile flow (Káldor and Pogátsa, 1959). Bile in turn may affect the secretion mechanism (Thomas and Crider, 1943) and promote the secretion of pancreatic juice. Tolbutamide, therefore, may promote digestion and absorption of proteins.

SUMMARY

In a double-blind trial, 20 patients with hypoproteinaemia, caused by malnutrition, malabsorption, or cirrhosis of the liver, were treated against a similar number of placebo controls. The results were assessed by sequential analysis. The criteria for assessment were subjective improvement, weight gain, reduction of oedema, and improvement in serum protein levels. A restricted closed design was chosen for the experiment. Of the 20 pairs which entered the trial, 15 pairs were in favour of tolbutamide, three pairs in favour of placebo, and two pairs were ties. The dose of tolbutamide was 0.5 g. twice daily for four weeks. There were no adverse effects and the drug was well tolerated. The beneficial effect of tolbutamide is discussed.

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