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CLINICAL TRIAL OF GLIBENCLAMIDE IN MATURITY-ONSET DIABETICS*

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Glibenclamide (HB 419) is known as a potent oral hypoglycemic agent in the sulphonylurea group.(1 - 3) The fact that sulphonylureas stimulate the pancreatic beta cells to release insulin is well established,(3 - 6) and are successfully used in the treatment of maturity-onset diabetics who still have well granulated beta cells. Müller et al analysed 5,053 glibenclamide treated patients from all investigators in Germany by means of identically itemized questionaires and concluded that it is more potent than tolbutamide, carbutamide and chlorpropamide.(7)

It is our attempt to study the hypoglycemic potency of glibenclamide, a newly introduced oral hypoglycemic agent, and also its side effects on hemogram, coagulogram. platelet adhesiveness, renal and thyroid functions in maturity-onset diabetics.

Materials and Methods

Selection of cases:

All patient of both sexes were selected from the diabetic clinic. The ages ranged between 25 to 75. Fifteen patients were previously untreated. Seven cases had previously been treated with Chlorpropamide and eight with chlorpropamide plus phenformin. These patients did not receive estrogen or other hormones and had no serious complications except for one who had mild proteinuren with normal blood urea nitrogen and creatinine.

The previously untreated patients were firstly controlled with a low-caloric diabetic diet. Glibenclamide* was prescribed only when there was persistent hyperglycemia.

The plan of investigation was as follows:

First visit : Complete history, physical examination body weight, height, complete blood count, urinalysis. fasting blood sugar, urea nitrogen, creatinine, liver function tests, cholesterol, electrocardiogram, chest film, maximum ^{131}I uptake, serum thyroxine, coagulogram, and platelet adhesiveness.

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*** Daonil, supplied by Farbwerke, Hoechst, Germany.

Second visit :	Suitable patients were selected. Glibenclamide was prescribed.
Third visit : (1 – 2 weeks after therapy)	Fasting blood sugar, body weight, interview for side effects.
Fourth visit : (1½ months)	Fasting blood sugar, body weight, physical examination, complete blood count, urinalysis, liver function tests, cholesterol, urea nitrogen, creatinine, interview for side effects.
Fifth visit : (3 months)	As the first visit.
Sixth visit : (6 months)	Regular follow up.

Some patients needed more frequent visits for evaluation of increasing or decreasing the daily dose. If a uniform response was achieved, maintenance dose was then prescribed.

Evaluation of dosage :

In fifteen previously untreated diabetics and seven diabetics previously treated with chlorpropamide, the initial dose of glibenclamide was 2.5 to 5.0 mg. once daily after breakfast. If control was unsatisfactory, elevation of the daily dose in steps of 2.5 mg. each week up to 10 mg. after breakfast and 5 to 10 mg. after evening meal was used.

Eight patients who were previously treated with chlorpropamide plus phenformin, were changed over to glibenclamide alone first. The initial dose was the same as the untreated group. Phenformin was added up to 300 mg. per day if satisfactory control can not be achieved within four weeks with a maximum daily dose of 15 mg. of glibenclamide

Criteria for evaluation of treatment :

The patients who maintained fasting blood sugars below 150 mg. per 100 ml. (Somogyi – Nelson) were considered to have good control, Those with blood sugars between 150 to 180 mg. per 100 ml. were considered to have fair control. Those whose blood sugar determinations were more than 180 mg. per 100 ml. were considered to be poorly controlled after a four – week trial of maximum daily dose of glibenclamide.

Results

The previously untreated group :

The effect of glibenclamide on blood sugar levels of 15 previously untreated diabetics was shown in Table 1. Twelve patients (80 percent) were well controlled with a single daily dose of 2.5 to 10 mg. of glibenclamide. Two cases (13.3 percent) were fairly controlled and one patient (6.7 percent) was poorly controlled with the maximum dose of 15 mg. per day of glibenclamide. for at least one month. These cases were better controlled when phenformin was added.

Hypercholesterolemia noted in 10 patients (67 percent) were found to be lower in all cases after treatment as shown in Table 2 and Figure 1.

TABLE 1 : Effect of Glibenclamide on Blood Sugar Levels of Previously Untreated Diabetics.

Diabetic Subjects			*Fasting Blood Sugar in mg. %*			*Dosage in mg.*	*Control of Diabetes*	
No.	*Hospital No.*	*Age*	*Before Rx*	*6 Weeks After Rx*	*12 Weeks After Rx*		*Before Rx*	*After Rx*
1	P.T. 104537/10	45	225	230	202	15.0	P	P
2	C.A. 112414/10	58	336	100	120	5.0	P	G
3	A.P. 67283/13	72	200	105	140	7.5	P	G
4	T.S. 30031/13	34	168	90	80	2.5	F	G
5	T.T. 44838/13	56	298	–	110	10.0	P	G
6	S.S. 117753/10	40	394	145	180	15.0	P	F
7	S.A. 49553/13	58	183	135	116	5.0	P	G
8	J.T. 39268/07	48	178	240	138	10.0	P	G
9	B.P. 42931/13	27	220	95	90	2.5	P	G
10	M.L. 50875/13	55	260	135	135	5.0	P	G
11	K.H. 52890/10	40	220	100	105	10.0	P	G
12	C.K. 60359/13	36	180	110	143	2.5	F	G
13	N.A. 59077/13	53	140	100	131	2.5	G	G
14	V.L. 73610/12	40	260	254	171	15.0	P	F
15	A.A. 71287/13	67	155	90	96	2.5	F	G
	Mean		227.80	128.60	130.46	7.33		
	Standard Deviation		71.00	66.96	34.11	4.86		

TABLE 2 : Serum Cholesterol Level Before and after Glibenclamide.

Diabetic Subjects		*Serum Cholesterol Level in mg. %*			*Dosage in mg.*
No.	*Age*	*Before Rx*	*6 Weeks After Rx*	*12 Weeks After Rx*	
1	45	288	275	265	15.0
2	58	310	215	200	5.0
3	72	170	200	173	7.5
4	34	390	218	175	2.5
5	67	270	235	250	10.0
6	40	195	183	288	15.0
7	58	360	420	287	5.0
8	48	410	275	301	10.0
9	27	143	195	147	2.5
10	55	308	210	–	5.0
11	40	220	140	154	10.0
12	36	378	182	273	2.5
13	53	330	320	252	2.5
14	40	350	188	180	15.0
15	67	150	203	182	2.5
Mean		284.80	230.60	208.46	7.3
Standard Deviation		89.64	68.80	78.46	4.9

The group previously treated with chlorpropamide :

The comparison of blood sugar levels in seven patients treated with chlorpropamide against glibenclamide was shown in Table 3. Three patients (42.9 percent) were better controlled with glibenclamide, three patients (42.9 percent) were equally controlled while one (14.2 percent) was less favourable with this drug.

The group previously treated with chlorpropamide plus phenformin :

Comparison of blood sugar levels in eight patients treated with chlorpropamide plus phenformin to glibenclamide alone or to glibenclamide plus phenformin was demonstrated in Table 4. Six cases (75 percent) were better controlled, including two cases who previously failed to the maximum dose of chlorpropamide plus phenformin, one (12.5 percent) was equally controlled and one (12.5 percent) was less favourable.

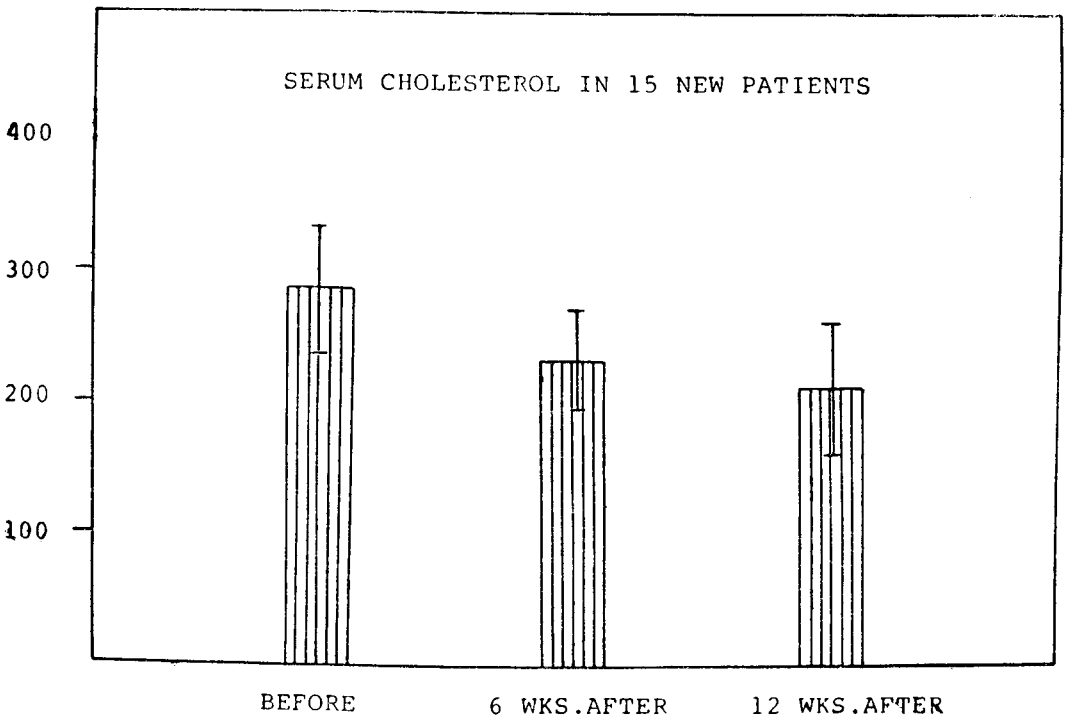

Fig 1.

The results of treatment of the previously untreated group, the group previously treated with chlorpropamide alone and the group previously treated with chlorpropamide plus phenformin against glibenclamide or glibenclamide plus phenformin were summarized in Table 5.

The overall results of the group previously treated with chlorpropamide and chlorpropamide plus phenformin, 60 percent were better controlled, 26.7 percent were equally controlled and 13.3 percent were less favourable. Increasing dose to 20 mg. was tried without benefit in three patients who failed to respond to 15 mg. of glibenclamide.

Mild and transient hypoglycemic symptoms were observed in 3 cases. All the symptoms disappeared after a reduction of dose of glibenclamide.

None of the patients had apparent side effects during a trial of this study.

There were no significant changes of the urinalysis, blood urea nitrogen, creatinine, serum glutamic oxaloacetic transaminase, total and direct bilirubin, thymol turbidity, alkaline phosphatase, maximum ^{131}I uptake and coagulogram. The hemoglobin concentration, white cell count, differential count remained within the normal ranges throughout the peroid of study.

Discussion

The machanism of action of glibenclamide as in the case of other sulphonylureas is through stimulation of insulin

TABLE 3 : Comparison of Blood Sugar Levels in Patients Treated with Chlorpropamide against Glibenclamide.

No.	*Hospital No.*	*Chlorpropamide*			*Glibenclamide*			*Comparison*
		Dosage mg.	*Blood Sugar mg. %*	*Result*	*Dosage mg.*	*Blood Sugar mg. %*	*Result*	
1	K.G. 81743/12		200	P	15	188	P	=
2	K.H. 38017/13	250	285	P	5	115	G	>
3	K.C. 113616/13	250	140	G	5	120	G	=
4	A.A. 50815/13	250	220	P	5	250	P	=
					15	145	G	
5	E.L. 48131/13	250	190	P	5	100	G	>
6	D.L. 35359/13	250	105	G	2.5	120	G	>
7	U.L. 121456/13	375	140	G	7.5	178	F	<
					15	167	F	

G = Good
F = Fair
P = Poor

= Equal
> Better
< Worse

TABLE 4 : Comparison of Blood Sugar Levels in Patients treated with Chlorpropamide plus Phenformin to Glibenclamide alone or to Glibenclamide Puls Phenformin.

No. Hospital No.	*Chlorpropamide + Phenformin*			*Glibenclamide + Phenformin*			*Comparison*
	Dosage mg.	*Blood Sugar mg. %*	*Result*	*Dosage mg.*	*Blood Sugar mg. %*	*Result*	
1 S.L. 035552/04	500 + 50	170	F	15 + 50	173	F	=
2 S.A. 018659/08	250 + 25	180	F	5 10	167 120	F G	> <
3 T.W. 23213/08	250 + 50	173	F	15 + 50	180	F	<
4 B.B. 058317/05	250 + 25	120	G	2.5	95	G	>
5 L.J. 86516/06	500 + 75	225	P	15 + 50	170	F	<
6 N.H. 26218/09	500 + 50	155	F	7.5	115	G	<
7 A.K. 61660/08	500 + 150	155	F	10 + 100	107	G	<
8 K.A. 058243/08	500 + 100	227	P	15 + 100	170	F	<

G = Good
F = Fair
P = Poor

= Equal
< Better
> worse

TABLE 5 : Result of Treatment.

Group	*Good*		*Fair*		*Poor*	
	No. of Cases	*Percentage*	*No. of Cases*	*Percentage*	*No. of Cases*	*Percentage*
Previously Untreated	12	80	1	6.7	2	13.3
Previously Treated with – Chlorpropamide	4	57	2	28.5	1	14.5
– Chlorpropamide + Phenformin	5	5	2	25	1	12.5

release from pancreatic beta cells of the islet of Langerhans.[3 - 6] It is an effective agent for the treatment of maturity – onset diabetes and compared favourably in this trial with chlorpropamide in some cases.

Christ, Heptner and Rupp[8] reported the maximum plasma level to be at 4 hours and fallen by over 95 percent within 24 hours. The glucose lowering effect of a single daily dose of 5 mg. in normal subject is found to last for 15 hours. In the human body, 45 percent of the drug is absorbed. Breakdown takes place by hydroxylation of the cyclohexyl group. The absorbed glibenclamide is exclusively eliminated in metabolised form via urine and bile. The principal metabolite of glibenclamide also has a hypoglycemic effect but it is weaker than that of the unaltered substance and said to be of no importance, when therapeutic dose is given.

Fearnley, Chakrabarti and Vincent[9] reported increased fibrinolytic activity in the patients treated with tolbutamide and chlorpropamide. In our study, glibenclamide had no significant effect on coagulogram after a trial for three months comparing with the base – line values.

Sulphonylureas were known to produce goiter in rat,[10 - 11] and impaired ^{131}I uptake in rat and in human.[12] There was however no significant change in the maximum ^{131}I uptake after glibenclamide in this study.

The lowering of cholesterol level after treatment was rather due to the better condition of diabetes than the direct effect of the drug.

In this study glibenclamide is found to be a new potent oral hypoglycemic agent in our diabetic patients, well tolerated and having no serious side effects. It is effective and safe hypoglycemic drug if the dosage is well adjusted. Doses beyond 15 mg. daily do not seem to produce a further increase in response. This study confirms the earlier works performed in Germany,[7] England and Australia.[14]

Summary

Glibenclamide was used in 30 maturity–onset diabetics for three to six months. In fifteen untreated subjects, 80 percent of the cases were well controlled with a single 2.5 to 10 mg. dose per day. Fifteen patients were switched from previously poorly or good controlled on chlorpropamide plus phenformin to glibenclamide. Sixty percent of the cases were better controlled with this drug, while 13.3 percent were less favourable and 26.7 percent were equally controlled. The maximum effective daily dose is 15 mg.

There were no significant changes of hemogram, coagulogram hepatic, renal function tests and maximum ^{131}I uptake in all patients during the period of treatment.

This study confirms that glibenclamide is a potent hypoglycemic agent, effective and safe if the dose is carefully adjusted.

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สรุป

ผลการทดลองใช้ ไกลเบนคลาไมด์ ในขนาด วันละ ๒.๕—๕ มิลลิกรัม รักษาผู้ป่วยเบาหวานที่เริ่มมีอาการเมื่อเป็นผู้ใหญ่ จำนวน ๓๐ ราย เป็นระยะเวลา ๓—๖ เดือน ปรากฏว่าในจำนวนผู้ป่วย ๑๕ ราย ที่ไม่เคยได้รับการรักษามาก่อน ยานี้สามารถควบคุมระดับน้ำตาลในเลือดได้ ในเกณฑ์ดีถึง ๘๐% ส่วนอีก ๑๕ ราย ซึ่งเปลี่ยนการรักษาจากคลอโปรปาไมด์ หรือคลอโปรปาไมด์ร่วมกับเฟนฟอมิน มาเป็นไกลเบนคลาไมด์นั้น ๖๐% ได้ผลดีกว่ายาเก่า ส่วนที่เหลือได้ผลดีเท่า ๒๖. ๗% และผลด้อยกว่า ๑๓.๓ %

ตลอดเวลาที่ใช้ยานี้ ผู้ป่วยทุกรายทนต่อยาได้เป็นอย่างดี ไม่พบอาการ หรือการแสดงอันไม่พึงประสงค์ รวมทั้งการเปลี่ยนแปลงที่แสดงว่ามีพิษต่อ ตับ ไต ต่อมธัยรอยด์ เม็ดโลหิต และการแข็งตัวของโลหิต

การทดลองนี้จึงสนับสนุนรายงานอื่น ๆ ที่กล่าวว่า ไกลเบนคลาไมด์ เป็นสารที่สามารถใช้ลดระดับน้ำตาลในเลือดได้อย่างดีและแรง โดยที่ใช้ได้อย่างปลอดภัยถ้าระวังขนาดที่ให้.