Is the Use of Sulphonylurea Derivatives in the Treatment of Diabetes Mellitus Dangerous?

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Summary. Grouping 651 diabetic deaths according to their treatment with diet alone, with diet and sulphonylurea tablets, with diet and small or large doses of insulin, we cannot discover any significant difference in the duration of diabetes from onset till death between patients treated by diet alone and those treated by diet and hypoglycaemic tablets. The longer duration of insulin-controlled diabetes is mainly due to the younger age of the patients at onset of the disease. Some other factors which may favour insulin treatment are discussed. Neither overweight nor hypertension explains the disparity in duration of diabetes between patients under diet or tablet therapy and others controlled by insulin.

Hypoglycaemia and side effects of sulphonylurea derivatives have been known for a long time and are not included in this study. — A critical review of the UGDP report does not give any justification for condemning tolbutamide therapy as dangerous. As in every really efficient medical treatment, sulphonylurea compounds should be used only when necessary, and then with the appropriate dosage, the necessary circumspection and good common sense!

L'emploi des dérivés sulfonylurées dans le traitement du diabète sucré est-il dangereux?

Résumé. 651 décès de diabétiques sont groupés selon leur traitement par régime seul ou par régime combiné avec des sulfonylurées ou régime avec insuline à faibles ou fortes doses. Il n'y a pas de différence significative quant à la durée du diabète depuis sa manifestation jusqu'à la mort entre le groupe traité par régime seul et celui traité par régime et tablettes hypoglycémiantes. La plus longue durée du diabète contrôlé par l'insuline s'explique surtout par le début de la maladie à un âge plus jeune. D'autres facteurs favorisant, peut-être, également l'efficacité de l'insulinothérapie sont mentionnés.

L'hypoglycémie et l'intolérance aux sulfonylurées sont connues depuis longtemps et ne sont pas incluses dans cet article. — Une étude critique du rapport de l'UGDP n'apporte aucune preuve du danger d'un traitement avec tolbutamide, pourvu que cette substance soit employée, comme tout médicament efficace, seulement pour les malades qui en ont vraiment besoin, à une dose appropriée et avec prudence!

Zusammenfassung. 651 Todesfälle von Zuckerkranken werden, entsprechend ihrer Behandlung mit Diät allein, mit Diät und Sulfonylharnstoffderivaten, mit Diät und kleinen oder großen Insulindosen gruppiert, wobei wir keinen signifikanten Unterschied in der Dauer des Diabetes von seiner Manifestation bis zum Tode zwischen den mit Diät allein und den mit Diät und blutzuckersenkenden Tabletten Behandelten feststellen können. Die längere Krankheitsdauer bei den Insulingruppen ist hauptsächlich durch das frühere Manifestwerden des Diabetes bedingt. Einige andere Faktoren, welche möglicherweise die Wirkung der Insulinbehandlung günstig beeinflussen, werden kurz erwähnt.

Hypoglykämie und Nebenwirkungen der Sulfonylharnstoff-Derivate sind seit langem bekannt und deshalb in dieser Studie nicht besprochen. — Eine kritische Prüfung des Berichtes der UGDP läßt keinen Beweis für eine gefährliche Wirkung des Tolbutamids erkennen, falls dieses, wie jedes andere wirksame Medikament, nur bei Patienten angewendet wird, die es wirklich benötigen, und dann in der passenden Dosierung, mit der notwendigen Vorsicht!

Key-words Diabetes, treatment, diabetes mortality, diabetes duration, tolbutamide, sulphonylurea, insulin therapy, diabetes prognosis.

Hypoglycaemia due to an overdose of a sulphonylurea compound or to the combination with a synergetic medication, as well as side effects like agranulocytosis, thrombocytopenia and others, are not within the scope of this report, which was prompted by a warning against the use of tolbutamide issued by the University Group Diabetes Program (UGDP).

Already in 1958, Haunz questioned the wisdom of substituting tolbutamide for insulin whenever possible; and in 1959, Lazarow and Treibergs observed in rats with alloxan-induced subclinical diabetes an increased mortality when treated by extremely large doses, i.e. 200–500 mg, of tolbutamide per kilogram bodyweight. Two years later, Bloodworth and Hamwi reported a high post mortem frequency of “microgran-

ulomas” in the myocardium of diabetics who had used sulphonylurea derivatives. However, the connection between this therapy and the histological changes has not been confirmed (Balodimos *et al.* 1968, Wellmann *et al.* 1963). Südhof and coworkers found coronary infarction more frequent in diabetics under sulphonylurea therapy than in others controlled by diet alone or by diet and insulin. Contrary to this, Keen & Jarrett observed, after five years treatment with tolbutamide the number of coronary infarction, angina pectoris, intermittent claudication, cerebral ischaemia and cardiac death was significantly smaller than in a control group. Also, clinical observations from the Joslin Clinic (Balodimos *et al.* 1967), of Paasikivi, of Feldman & coworkers revealed no increase in mortality or pre-

valence of circulatory disturbances in diabetics under tolbutamide therapy.

Evidently, the literature is contradictory. When the UGDP reported an increased mortality in tolbutamide-treated diabetics, I tried to obtain a personal unbiased opinion by reviewing 651 diabetic deaths observed amongst my private patients. 236 of them had died from cardiac insufficiency, coronary thrombosis, myocardial degeneration or hypertensive heart disease (cardiac death group).

According to their treatment during the last few years, these patients were classified in 5 groups:

Group 1. 83 diabetics treated by diet alone,

Group 2. 63 patients treated with diet and sulphonylurea,

Group 3. 242 patients treated by diet and small doses of insulin, i.e. not more than 30 units per day under normal conditions, even if they needed larger quantities during intercurrent infections or injuries,

Group 4. 225 diabetics using diet and more than 30 units of insulin per day,

Group 5. 38 cases of labile diabetes under dietary and insulin therapy.

Each group is subdivided into two subgroups, those with cardiac deaths, and those dead from other causes.

The frequency of *cardiac deaths* is, according to *Table 1*, higher in group 1 (diet alone) than in all the others. The difference between the tablet- and the low dose insulin group is not impressive and is statistically insignificant.

Table 1. Frequency of cardiac deaths

	Total number	Cardiac deaths total	per cent
Group 1			
Rx: diet alone	83	39	47
Group 2			
Rx: diet + tablets	63	26	41
Group 3			
Rx: diet + insulin in small doses	242	94	39
Group 4			
Rx: diet + insulin in larger doses	225	69	31
Group 5			
Rx: diet + insulin labile diabetes	38	8	21

Table 2 summarizes the *average ages at onset, at death*, and the *average duration of diabetes* in the five groups and their subgroups. The duration of diabetes is the same in the cardiac death groups treated by diet alone and the one with diet and tablet therapy, the difference in age is statistically not significant, whilst those dead from other causes lived a shorter time in the tablet group. However, this is not important, since the age at onset and at death were higher in this group. Furthermore, tablets were used for about 15 years only,

whereas the other groups include diabetics whom we observed for a much longer period. A certain number of sulphonylurea-treated patients develop secondary resistance to the treatment and become, sooner or later, an insulin-needing group. Therefore, it is rather surprising not to find a more marked discrepancy between the tablet- and the diet alone group.

Table 2. Age at onset, age at death and duration of diabetes

	Number	Age at onset	Age at death	Duration
Group 1				
total	83	57 ± 11	69 ± 9	12 ± 9
cardiac deaths	39	58 ± 11	69 ± 10	11 ± 9
other deaths	44	57 ± 10	69 ± 8	13 ± 10
Group 2				
total	63	59 ± 10	70 ± 10	11 ± 8
cardiac deaths	26	55 ± 14	67 ± 9	11 ± 9
other deaths	37	62 ± 9	72 ± 9	10 ± 7
Group 3				
total	242	54 ± 11	70 ± 10	16 ± 9
cardiac deaths	94	53 ± 11	70 ± 9	16 ± 10
other deaths	148	55 ± 8	70 ± 11	15 ± 9
Group 4				
total	225	48 ± 9	65 ± 10	17 ± 9
cardiac deaths	69	45 ± 10	65 ± 10	20 ± 8
other deaths	156	50 ± 15	65 ± 15	15 ± 10
Group 5				
total	38	24 ± 15	48 ± 18	23 ± 10
cardiac deaths	8	35 ± 10	63 ± 6	28 ± 7
other deaths	30	22 ± 10	44 ± 19	22 ± 10

Table 3. Distribution of sex, frequency of obesity and of hypertension

	Male	Female	Over-weight	Hypertension
	per cent	per cent	per cent	per cent
Group 1				
total	77	23	44	62
cardiac deaths	77	23	32	67
other deaths	77	23	54	58
Group 2				
total	63	37	48	54
cardiac deaths	69	31	57	50
other deaths	59	41	43	57
Group 3				
total	52	48	33	58
cardiac deaths	54	46	33	61
other deaths	51	49	34	55
Group 4				
total	59	41	45	49
cardiac deaths	68	32	54	51
other deaths	54	46	41	47
Group 5				
total	53	47	10	45
cardiac deaths	62	38	14	17
other deaths	50	50	9	52

The decidedly longer duration in insulin-treated diabetes is, at least partly, due to the earlier onset of diabetes. Closer medical supervision may be another factor, and there is the possibility, that insulin has other beneficial actions besides lowering the blood sugar concentration. To my knowledge, this has not

been proven yet, but we have the clinical impression, that, in progressive retinopathy and in cases with infected gangrene, insulin is more efficient than sulphonylurea compounds, even if the latter permit excellent control of blood sugar.

Table 3 shows the *sex distribution* with a decided preponderance of male diabetics, whilst in the UGDP study, women outnumbered men.

Overweight of more than 10 per cent, is a little more frequent in group 1 and 2, i.e. in diabetics with manifestation later in life than in the insulin groups. It does not explain the shorter duration of diabetes in the diet alone or diet and tablet treated diabetics, since in group 4 overweight is also not infrequent.

Hypertension, i.e. more than 160 mm Hg systolic or more than 90 mm Hg diastolic pressure on repeated examinations of resting, recumbent patients, is most common in cardiac deaths of diabetics treated by diet alone. Its frequency in the group with tablet therapy is not outstanding. In spite of the relatively low average age at onset of group 5, its subgroup "other causes of death" is often combined with high blood-pressure as a result of the prevalence of terminal nephropathy in growth-onset diabetes.

Our data do not corroborate the results of the UGDP study; we are unable to prove a shortening of the duration of diabetes in the sulphonylurea treated group.

Examining the UGDP report more carefully, we found a marked preponderance of female patients. Under cardiovascular deaths are listed myocardial infarction, sudden death, other cardiac conditions, cerebral ischaemia, pulmonary embolism and peripheral vascular disturbances. Compared with the placebo group, those treated by tolbutamide had, already at the beginning of the study more frequently a history of digitalis medication, of angina pectoris, of significant electrocardiographic abnormalities, hypercholesterolaemia (> 300 mg per cent), pathology on fundus photography, calcification of peripheral arteries and absence of one or more arterial pulses. The assignment to the tolbutamide — or placebo — or one of the insulin groups was arbitrary, and the dosage of tolbutamide fixed at 1.5 gram per day, regardless of the need of the patient. After onset of the treatment, the fasting blood sugar values dropped, but rose again after 1 year, and stayed high, thus proving that the diabetes was not well controlled. In opposition to this, our patients were treated

by sulphonylurea compounds only when they were in need of it, when dietary therapy alone was insufficient, and the dosage was currently adapted to the requirement of the patient, carefully avoiding hypoglycaemia.

As far as I can see, the UGDP study suggests that tolbutamide should not be used in patients who do not need it, nor in doses which disregard the requirements of the patient and keep the diabetes uncontrolled. I just wonder what would happen, if any other, really active medication were applied to patients who do not need it, and in inadequate dosage, for instance digitalis?

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