JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2018, 69, 4, 647-649
www.jpp.krakow.pl | DOI: 10.26402/jpp.2018.4.15

Short Communication

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HYPOGLYCEMIC SIDE EFFECTS OF SULFONYLUREAS AND REPAGLINIDE IN AGEING PATIENTS - KNOWLEDGE AND SELF-MANAGEMENT

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Insulinotropic oral antidiabetics (OAD) such as sulfonylureas and (SU) glinides are among the frequently prescribed OAD. Side effects are the potential to induce hypoglycemias and weight gain. The aim was to assess the self-managing skills in case of a hypoglycemic event in an elderly type 2 diabetic patient population. In a 2-year period, 160 hospitalized patients (mean age 77.4 years) under insulinotrophic OAD were interviewed using a standardized questionnaire. Additionally, possible dementia was evaluated by using the Mini-Mental State Examination (MMSE) and the Clock-Drawing Test (CDT). The mean HbA1c was 7.6%. MMSE and CDT did intraindividually correlate well and 23.8% of the patients had moderate dementia (10 – 20 points MMSE), 13.1% had severe dementia (0 – 10 points MMSE) at the time of the survey. When under treatment with a sulfonylurea, only 16.0% of patients were aware of the potential hypoglycemia-inducing side effect. Moreover, only 11.8% of patients treated with a combination of a sulfonylurea and insulin knew this side effect of the OAD. The awareness of the side effects of repaglinide was 21.6% (without insulin therapy) versus 21.4% in the insulin-comedicated group. Only 42.6% of patients treated with sulfonylureas or repaglinide knew how to act in the case of hypoglycemia. Even under comedication with insulin, only in 41.2% of the respondents in the comedicated group knew how to take action if they were to experience hypoglycemia. Our findings raise concerns and demonstrate, that the self-managing skills in an elderly patient group are not good, which may become an increasing problem in an ageing population. The prescription or the re-prescription of insulinotropic OAD needs to be adapted to the current cognitive situation and re-evaluated regularly.

Key words: *diabetes mellitus, oral antidiabetics, sulfonylureas, glinides, hypoglycemia, elderly, dementia*

INTRODUCTION

Insulinotropic oral antidiabetics (OAD) such as sulfonylureas (SU) or the prandial glucose regulators, also known as glinides, are in wide clinical use and are still part of the standard drugs used in diabetes care worldwide. In the case of SU, their potentially negative cardiovascular effects are controversially discussed (1). The further potential disadvantages of these drugs are their hypoglycemia-inducing properties, and weight gain. SU are the „oldest" OAD introduced into the market by the pharmaceutic industry and in these days, the glucose-lowering effect was the most important therapeutic target. However, with the worldwide increase in obesity (and its metabolic complications) in the last decades, new antidiabetic drugs are expected to be at least weight-neutral (such as the dipeptidyl-peptidase 4 inhibitors) or ideally weight-reducing (such as metformin, sodium glucose co-transporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists). Apart from already established drugs, several promising, yet experimental approaches such as orexin A (2) are on their way. The evaluation of the yet established therapies should also adress their safety, especially in elderly patients: since the population in industrialized countries is aging and a progressive cognitive impairment can be assumed, we were particularly interested in the patients' state of awareness concerning the properties and risks of insulinotropic OAD and the knowledge of how to act in case of hypoglycemia. Our aim was to assess the self-managing skills in case of hypoglycemic events in an elderly patient population treated with insulinotropic OAD alone or in combination with an insulin therapy.

MATERIALS AND METHODS

In a 2-year period all (n = 160) hospitalized patients (82 female, 78 male) under antidiabetic therapy with SU (66%, glimepiride or glibenclamide) or glinides (33%, repaglinid) (and other oral antidiabetic treatments; n = 44 had additional insulin therapy) were examined. The reason for hospitalization was not relevant and, eventually, only 10% were admitted due to insufficient glycemic control. The mean age of the patients was

77.4 years (range 47 – 101 years). Half of the patients had suffered from diabetes mellitus and had been taking insulinotropic OADs for more than 10 years. The analysis of the patients' care situation showed that the overwhelming majority (n = 130) lived in a home environment without professional outpatient care. Twelve patients also lived at home, but were supported by outpatient care in everyday life matters. Eighteen patients were housed in a nursing home.

After giving informed consent by the patients or their legal guardians, the patients were interviewed using a standardized questionnaire. Additionally, possible dementia was evaluated by using the Mini-Mental State Examination (MMSE) (3) and the Clock-Drawing Test (CDT) in the test version. A score < 5 raises suspicion towards dementia (4).

RESULTS

The mean HbA1c was 7.6%. Mini-Mental State Examination and the Clock-Drawing Test did intra-individually correlate well and 23.8% of the patients showed moderate dementia (10 – 20 points MMSE), 13.1% had severe dementia (0 – 10 points MMSE) at the time of the survey. This is the reason, why the duration of diabetes mellitus and its therapy could not be reported exactly in some cases (*Table 1*). A history of severe hypoglycemic events was reported by 52.4% of patients in the sulfonylureas group and 46.4% in the repaglinide group (since this was a retrospective survey based on the memory of patients and existing records in our clinic, severe hypoglycaemia was defined as events related to hypoglycemia requiring intervention).

Some sulfonylureas patients (37.4%) and 54.7% in the repaglinide group stated that they had received diabetes training. In the sulfonylureas group with additional insulin therapy 48.3% had received diabetes coaching. In the repaglinide group with additional insulin therapy 64.3% had received counseling.

That said, of concern was the level of knowledge about the insulinotropic OAD. These findings are reported in *Table 1* together with the anthropometric data of the study group split on the basis of the OAD used. The table demonstrates, that the main hypoglycemia-inducing side effect of the oral antidiabetic medication was generally poorly known among the patients. When under treatment with a sulfonylurea, only 16.0% of patients were aware of the potential hypoglycemia-inducing side effect of this OAD. Moreover, only 11.8% of patients treated with a combination of a sulfonylurea and insulin knew this side effect of the OAD prescribed to them. The awareness of the side effects of repaglinide was slightly higher in this study group with 21.6% (without insulin therapy) versus 21.4 percent in the comedicated group.

Only about the half of patients treated with sulfonylureas or repaglinide knew how to act in the case of hypoglycemia. Even under comedication with insulin the knowledge was not better (*Table 1*).

Patients who were treated for their diabetes mellitus not only by the family physician but also by a diabetologist (about 25% in both groups) performed only slightly and not significantly better in the interviews (data not shown).

Table 1. Anthropometric data of the study group split on the basis of the oral antidiabetic drugs (OAD) used average plus standard deviation (Av./SD).

		Sulfonylurea without insulin				**Sulfonylurea with insulin**				**Repaglinide without insulin**				**Repaglinide with insulin**			
		n		**%**		**n**		**%**		**n**		**%**		**n**		**%**	
Number		75		46.9%		34		21.3%		37		23.1%		14		8.8%	
Sex	male	39		50.0%		16		20.5%		18		23.1%		5		6.4%	
	female	36		43.9%		18		22.0%		19		23.2%		9		11.0%	
		Av.	**SD**	**Max.**	**Min.**	**Av.**	**SD**	**Max.**	**Min.**	**Av.**	**SD**	**Max.**	**Min.**	**Av.**	**SD**	**Max.**	**Min.**
Age (years)		76.5	11.2	101.0	50.0	77.4	9.4	92.0	56.0	79.8	7.4	93.0	57.0	75.5	13.2	91.0	47.0
MMSE score		24.2	8.1	30.0	0.0	22.2	10.1	30.0	0.0	19.6	11.1	30.0	0.0	26.0	3.4	30.0	20.0
Clock-Drawing Test Score		5.5	2.5	7.0	0.0	5.0	2.8	7.0	0.0	4.2	3.1	7.0	0.0	6.1	1.5	7.0	2.0
		n		**%**		**n**		**%**		**n**		**%**		**n**		**%**	
Duration of diagnosis	unknown	11		14.7%		2		5.9%		6		16.2%		1		7.1%	
	< 5 years	12		16.0%		4		11.8%		3		8.1%		3		21.4%	
	5 – 10 years	18		24.0%		8		23.5%		8		21.6%		3		21.4%	
	> 10 years	34		45.3%		20		58.8%		20		54.1%		7		50.0%	
Duration of use of OAD	unknown	9		12.0%		3		8.8%		8		21.6%		2		14.3%	
	< 5 years	15		20.0%		5		14.7%		5		13.5%		4		28.6%	
	5 – 10 years	21		28.0%		7		20.6%		9		24.3%		2		14.3%	
	> 10 years	30		40.0%		19		55.9%		15		40.5%		6		42.9%	
Knowledge of hypoglycemia-inducing potential	no	63		84.0%		30		88.2%		29		78.4%		11		78.6%	
	yes	12		16.0%		4		11.8%		8		21.6%		3		21.4%	
Ability to treat hypoglycemia	no answer	6		8.0%		4		11.8%		5		13.9%		1		7.1%	
	correct	31		41.3%		16		47.1%		18		50.0%		8		57.1%	
	not correct	38		50.7%		14		41.2%		13		36.1%		5		35.7%	

DISCUSSION

Several patients treated with potentially hypoglycemia-inducing OAD showed different degrees of dementia and even among those who have not shown any signs of dementia some are not aware of this side effect and do not know how to behave should such an event occur. The finding that the awareness on the risk of hypoglycemia and the self-therapy in case of such an event was slightly worse in the sulfonylureas group under co-medication with insulin compared to sulfonylureas therapy without insulin led us to hypothesize that these patients were at a later stage of their disorder and thus older and more demented. However, this cannot be supported by the comparison of age and the results in the testings for dementia, but the number of patients under co-medication with insulin was realtively low. However, as for the whole population, is most likely that the general lack of knowledge is the result of the increasing cognitive impairment of the patients. The notion that this side effect had never been addressed by a physician is rather unlikely. To mitigate the risk of hypoglycemia it is not only necessary to constantly re-educate the patients but also do the same with relatives and healthcare providers, since the patients' ability to remember such risks may be limited due to their increasing cognitive impairment.

The number of patients examined is relatively small but from our point of view, the findings are representative for the reality of medical care in a rural area as seen in a municipal hospital. The mean age of patients in the departments of internal medicine in our clinic is 67 years. The observation, that the patient sample under insulinotropic OAD therapy was 10 years older, reflects the fact, that metformin is generally accepted as - given no contraindication - the first-line drug in the therapy of type 2 diabetes due to the positive effects on weight and other facettes of the metabolic syndrome. Metformin therapy does also have its merits on components of the metabolic syndrome in gestational diabetes (5). That said, insulinotropic OAD are not regarded as first-line drugs any more and thus, the number of *de novo* prescriptions is declining (6). In case of therapy with insulinotropic OAD, the re-prescription seems to be handled rather uncritically regarding the cognitive situation. That said, our findings highlight the concern that more and more elderly patients are put at a potentially life-threatening risk. Among older adults with diabetes, a bi-directional association between hypoglycemia and dementia has been reported (7). The increased frequency of hospitalizations due to hypoglycemic events is also becoming an increasing burden on the healthcare systems (8). These findings should prompt the attending physicians to adapt the re-prescription of insulinotropic OAD to the current cognitive situation and to re-evaluate it regularly.

In conclusion, many elderly patients - although previous counseling can be assumed, especially in patients under co-medication with insulin - do not remember or know the hypoglycemia-inducing effects of sulfonylureas or glinides, and do not know how to act in such a situation. Due to the discussion on potentially adverse cardiovascular effects of sulfonylureas and side effects such as hypoglycemia and weight gain, the prescription rates of insulinotropic OAD are declining, since other OAD without these side-effects are available. However in case of elderly patients already treated with insulinotropic OAD since a longer time, the assumable progressive cognitive impairment puts them at a rising risk for adverse events such as hypoglycemia combined with an inability to take action in such a situation. Further therapy with such drugs regularly needs to be reevaluated with respect to the cognitive performance.

Acknowledgement: The authors are grateful to A. Anemueller, K. Kaiser and A. Ortloff for their eminent help in the patient interviews and the data collection.

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Received: August 11, 2018
Accepted: August 30, 2018

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The aim was to assess the self-managing skills in case of a hypoglycemic event in an elderly type 2 diabeti â€¦Â Side effects are the potential to induce hypoglycemias and weight gain. The aim was to assess the self-managing skills in case of a hypoglycemic event in an elderly type 2 diabetic patient population. In a 2-year period, 160 hospitalized patients (mean age 77.4 years) under insulinotrophic OAD were interviewed using a standardized questionnaire.Â The awareness of the side effects of repaglinide was 21.6% (without insulin therapy) versus 21.4% in the insulin-comedicated group. Only 42.6% of patients treated with sulfonylureas or repaglinide knew how to act in the case of hypoglycemia. Drawbacks to insulin therapy include the side effects of weight gain, hypoglycemia and patient reluctance to use insulin. MCombinations of oral hypoglycemics and insulin are likely preferable to treatment with insulin alone.Â Repaglinide GLUCONORM MRepaglinide is rapid but short acting and is useful in lowering PPBG and HbA1c . It has a lower risk of hypoglycemia than sulfonylureas and appears to be well tolerated. It may be especially useful in individuals with irregular eating habits.Â wa variety of 2-drug (& sometimes 3 drug) combinations may be considered wcombination of repaglinide and sulfonylureas not usually recommended.Â Management of patients with hypertension and diabetes mellitus: advances in the evidence for intensive treatment. Common side effects of Prandin include low blood glucose (hypoglycemia), headache, nausea, vomiting, diarrhea, constipation, stomach pain, back pain, upper respiratory infections, chest pain, and hair loss. Consult your doctor before taking Prandin if pregnant or breastfeeding.Â Like sulfonylureas, Prandin stimulates cells in the pancreas to produce insulin.Â Prandin (repaglinide) is a meglitinide used to lower blood sugar (glucose) in patients with type 2 diabetes. Common side effects of Prandin include low blood glucose (hypoglycemia), headache, nausea, vomiting, diarrhea, constipation, stomach pain, back pain, upper respiratory infections, chest pain, and hair loss. No adequate human studies on the effects of Prandin on the fetus have been done.