Sulfonylureas and Mortality Risk

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Abstract

Sulfonylureas are a group of anti-diabetic medications, commonly used in the management of Type 2 diabetes mellitus. Sulfonylureas have been used as a second line option after metformin world-wide for better glycaemic control for the last few decades. Recently newer evidence has emerged highlighting the adverse effects of sulfonylureas in terms of increased cardiovascular risks, stroke risk and increased mortality overall. Despite this Sulfonylureas are still used commonly as being cost effective.

This article focuses on literature review giving evidence around sulfonylureas and associated mortality risks.

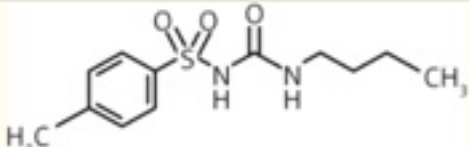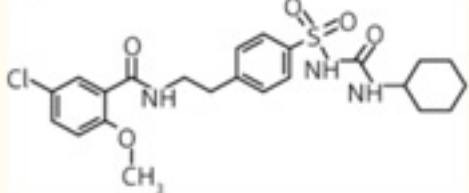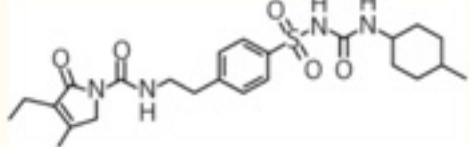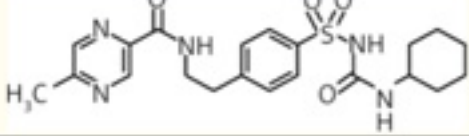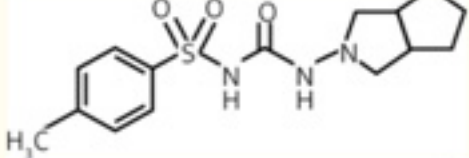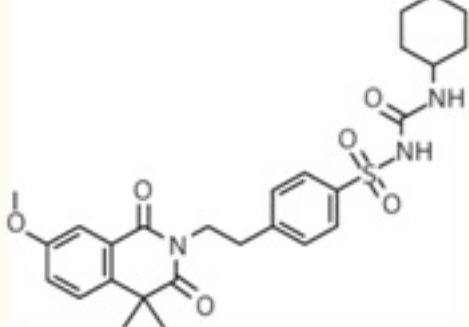Key words: sulfonylureas, mortality, evidence base

Introduction

Sulfonylureas (SU) are a group of medications used in the treatment of Type 2 diabetes mellitus (T2DM). Sulfonylureas were first discovered in 1942 when Marcel Janbon found that some sulfonamides lowered blood sugar levels in experimental animals. Carbutamide was the first SU synthesised and used in the management of T2DM but was withdrawn subsequently due to its bone marrow toxicity. Since the 1960s, several sulfonylureas have been made available and are classified into first and second generations varying in their pharmacodynamic and pharmacokinetic properties (Figure-1) (1).

First generation SU can cause more hypoglycaemia and are not prescribed as frequently nowadays. The second generation SU have replaced the first generation in clinical use as these can be used in smaller doses and have more potency and safety as compared to the first generation SU. Also, second generation SU are usually preferred when there is poor kidney function (2)(3). The first generation group have longer half-lives, more risk of hypoglycemia and more drug interactions as compared to the second generation group (4).

Sulfonylureas act by increasing the release of insulin from Pancreas and are only effective when there is residual pancreatic β-cells function and this is the reason for their effectiveness in T2DM rather than Type 1 diabetes. SU act by blocking the K-ATP channels in pancreatic β-cells, causing reduced K+ permeability and increasing intracellular depolarisation. This causes opening of voltage dependent Ca+ channels causing calcium influx in pancreatic β-cells, triggering exocytosis of preformed Insulin granules within pancreatic β-cells (Figure-2) (1) (5).

Although Sulfonylureas are commonly used in the management of T2DM worldwide, they do carry potential side effects which include risk of hypoglycemia, weight gain and allergic reactions during the first 6 to 8 weeks of treatment (6). This literature review has looked at the effects of SU in terms of cardiovascular mortality, stroke and risk of death.

Various generations of sulfonylureas

Molecules	Gen.	Dose [mg]	Duration of action* T1/2	Activity of metabolites T1/2	Elimination	Structure
Tolbutamide	I	500–2000	Short 4.5 to 6.5 h	Inactive	Urine ≈ 100%	
Glibenclamide	II	2.5–15	Intermediate to long 5 to 7 h	Active 10 h	Bile ≈ 50%	
Glimepiride	II	1–6	Intermediate 5 to 8 h	Active 3 to 6 h	Urine ≈ 80%	
Glipizide	II	2.5–20	Short to intermediate 2 to 4 h	Inactive	Urine ≈ 70%	
Gliclazide	II	40–320	Intermediate 10 h	Inactive	Urine ≈ 65%	
Gliquidone	II	15–180	Short to intermediate 3 to 4 h	Inactive	Bile ≈ 95%	

*Short duration of activity means < 12 h, intermediate 12–24 h, long over 24 h.

Figure 1 – Taken from Sola D et al – Various generations of Sulfonylureas and their properties (1)
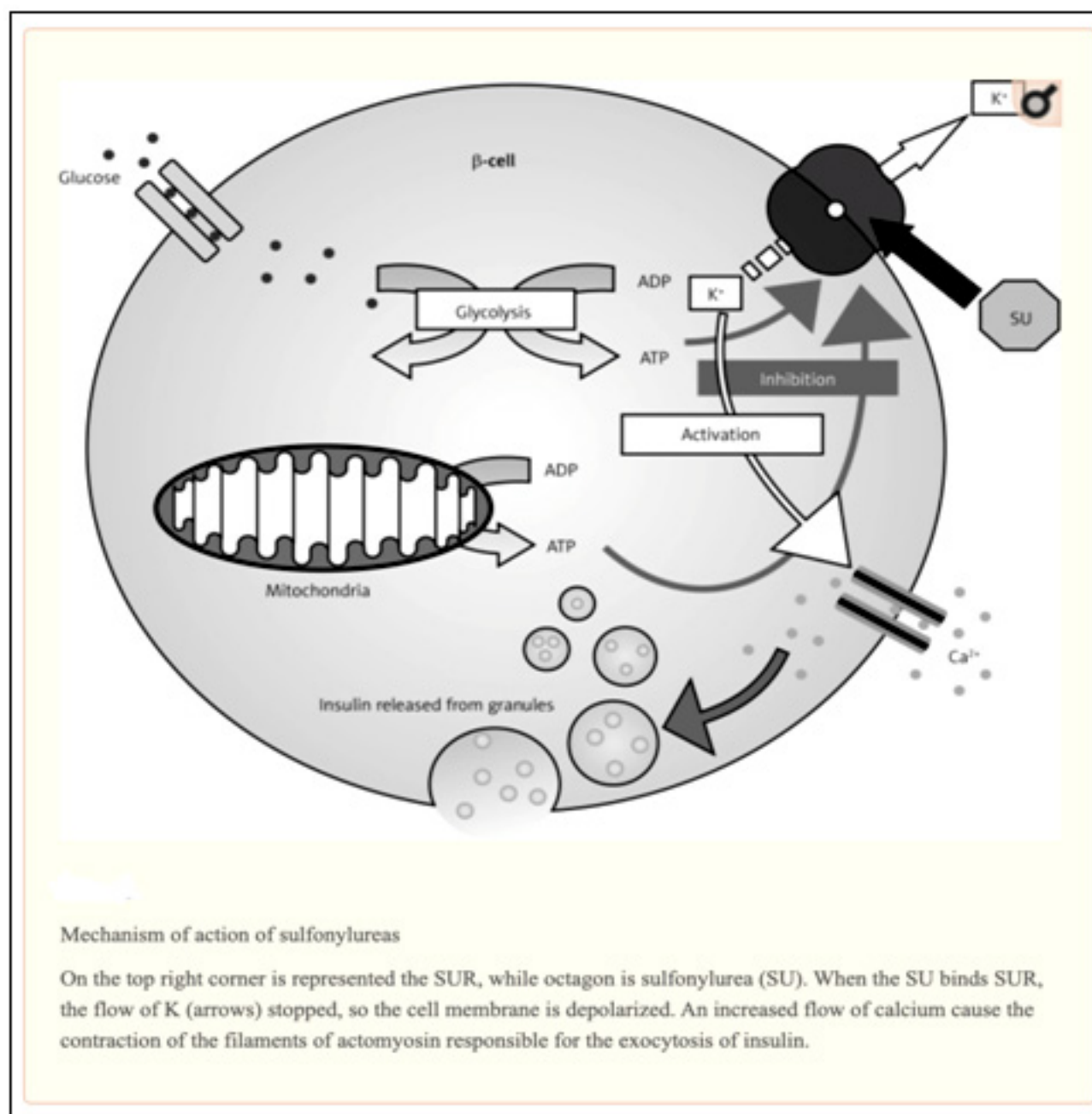
Figure 2 – Taken from Sola D et al – Mechanism of Action of Sulfonylureas

Literature Review

It is well established that T2DM itself is associated with various complications including increased risk of cardiovascular mortality as well as morbidity. Apart from this risk associated with T2DM, there is an increased interest if certain antidiabetic medications can influence the cardiovascular risks and outcomes. As sulfonylureas have been the second most commonly used antidiabetic medications after metformin, there have been increased concerns around their cardiovascular safety profile (7). The University Group Diabetes Program (UGDP) conducted a long-term prospective trial, evaluating the effects of Tolbutamide, a first generation SU in prolonging patients' life. The study showed that the Tolbutamide treated group had a higher risk of cardiovascular mortality and all-cause mortality than any of the other treatment groups (8).

Douros et al's population-based cohort study looked at patients with T2DM who were already on metformin and were either switched to SU or had SU added as second line treatment. The study looked at if there was an increased risk of ischemic stroke, myocardial infarction, cardiovascular death and all cause mortality with SU use. The study looked at patients with T2DM who started metformin between 1998 to 2013. After a mean follow up of 1.1 years, SU use was associated with an increased risk of myocardial infarction (incidence 7.8 vs 6.2 per 1000 patients), increased all cause mortality (27.3 vs 21.5), increased risk of ischemic stroke (6.7 vs 5.5) and increased cardiovascular deaths (9.4 vs 8.1) (9).

A systematic review of 31 published observational studies looked at the risk of acute myocardial infarction (AMI) with use of sulfonylureas, metformin and glitazones use in T2DM patients. Sulfonylurea use increased AMI risk

by 24% when compared to metformin. The relative risk of AMI for sulfonylureas vs metformin was 1.24 (CI 1.14-1.34) (10). Azoulay et al (2017) described 6 observational studies with no major biases that assessed the cardiovascular events and all-cause mortality with sulfonylurea vs metformin use and looked at major adverse cardiovascular events (MACE) and myocardial infarction. A summary of all 6 observational studies is given as under showing relative risks (7).

A meta-analysis of 115 selected trials with a duration of 6 months, compared sulfonylureas with other oral anti-diabetic medications. From 115 selected trials, 62 trials reported information on major cardiovascular events and 30 reported one event at least. In T2DM, SU use was associated with increased risk of stroke and increased mortality (11). Garratt et al (1999) looked at the impact of SU on outcomes in diabetic patients undergoing direct coronary angioplasty after acute myocardial infarction. The trial looked at 67 diabetic patients taking oral SU and 118 patients not on SU. The results showed that the hospital mortality was significantly high among the SU treated group vs those not on SU (24% vs 11%). The study showed sulfonylurea usage was associated with a higher risk of in hospital mortality among diabetic patients having coronary angioplasty after myocardial infarction (12).

Discussion

Sulfonylureas have been used as second line anti-diabetic medications in the treatment of T2DM for a long time. Despite strong recommendations, in many instances SU are also used as first line anti-diabetic medications where metformin is not appropriate to use (13). As per the previous American Diabetes Association (ADA) and European Association for the study of diabetes (EASD) published guidelines, SU were recommended as second line agents in the management of T2DM after metformin

and have been widely used as anti-diabetic medication worldwide (14). SU represent an important class of drug in patients who do not achieve ideal glucose control on metformin therapy alone. SU are inexpensive and per dose cost is much lower than the newer anti diabetic medications including Sodium glucose co-transporters 2 inhibitors (SGLT-2i).

Recently, a lot of evidence has emphasized that SU are associated with increased risk of cardiovascular disease, risk of stroke and overall risk of mortality. Many clinical trials and observational studies have shown similar results as discussed in literature review.

A large retrospective cohort study looked at risk of cardiovascular death and risk of heart failure among 253, 690 patients started on SU vs metformin from 2001 to 2011. There was an increase in cardiovascular risk in the SU group compared to metformin initiators, hazards ratio 1.21 (CI 1.13 – 1.30) (15). A population-based cohort study of adults ≥ 35 years of age with T2DM between 2004 to 2014, looked at MACE with SU use within different ethnic groups. With a total number of 208,870 patients, 13,755 were South Asians, 172,244 were Canadians and 22,871 were Chinese population; the MACE and mortality were higher in the South Asian and Chinese population (16).

Similar results have been seen with different studies as mentioned in the literature review above. In general SU use is associated with increased risk of ischemic stroke, myocardial infarction, risk of overall mortality in patients with T2DM who are already at increased risk of these complications given their diabetes (7) (9)(12).

Author	Study design	Comparison	Outcome(s)	Relative risk[a] (95% CI)
Cardiovascular events				
McAfee et al. (21)	Cohort	Sulfonylureas vs. metformin	MI and coronary revascularization	1.30 (1.04–1.61)
Schramm et al. (38)	Cohort	Glimepiride vs. metformin	MACE	1.32 (1.24–1.40)
		Glyburide vs. metformin	MACE	1.19 (1.11–1.28)
		Glipizide vs. metformin	MACE	1.27 (1.17–1.38)
		Tolbutamide vs. metformin	MACE	1.28 (1.17–1.39)
Roumie et al. (43)	Cohort	Sulfonylureas vs. metformin	MACE	1.16 (1.08–1.25)
All-cause mortality				
Gulliford et al. (11)	Cohort	Sulfonylureas + metformin vs. metformin	All-cause mortality	0.95 (0.64–1.40)
Azoulay et al. (29)	Nested case-control	Sulfonylureas vs. metformin	All-cause mortality	1.43 (1.33–1.56)
Wheeler et al. (46)	Cohort	Glyburide vs. metformin	All-cause mortality	1.38 (1.27–1.50)
		Glipizide vs. metformin	All-cause mortality	1.55 (1.43–1.67)

MACE, major adverse cardiovascular event; MI, myocardial infarction. [a]Relative risk is used as a generic term for rate ratio, HR, and odds ratio.

Figure 3 – Taken from Azoulay et al – Observational studies comparing cardiovascular safety of SU (7)

Conclusion

Sulfonylureas have been in use for decades as second line medications in management of T2DM. Although they are quite effective medicines, their use has been associated with more risk of mortality and deaths in terms of cardiovascular disease and stroke. Their use should be limited as newer antidiabetic medication groups now can be used and are recommended in the management of T2DM. Metformin still remains the drug of choice in T2DM and for further glycaemic control newer medicines are a better option.

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