

Hypoglycemia with insulin and sulfonylureas

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Clinical Inquiries question

In patients with type 2 diabetes mellitus (T2DM), does the combination of insulin and sulfonylurea (SU) increase the risk of hypoglycemia?

Evidence-based answer

The incidence of severe hypoglycemia in patients with T2DM taking insulin alone, SU alone, or the combination of insulin and SU is low (strength of recommendation [SOR] A based on a systematic review of randomized controlled trials). The combination of insulin and SU in patients with T2DM does increase the risk of hypoglycemia; however, the clinical significance of this risk is small (SOR B based on 4 large retrospective cohort studies). Of note, patients 65 years and older are at an increased risk of hypoglycemia compared with younger patients, although the clinical significance has not been specified (SOR B based on 2 large retrospective cohort studies).

Evidence summary

A Cochrane systematic review included 8 randomized controlled trials with 239 patients followed from 12 weeks to 1 year, and compared insulin with insulin and SU. Hypoglycemic episodes were defined differently in all trials and ranged from mild to severe. Seven of 8 trials reported the same or fewer hypoglycemic events in patients taking insulin alone compared with insulin and SU. The range of hypoglycemic events was 2.0 to 2.6 events per participant taking insulin alone compared with 2.2 to 6.1 events per participant for patients taking insulin and SU. Most of these events were mild and severe events were rare.¹


A large retrospective Danish study included 27 991 patients, 16 910 of whom were taking metformin and insulin and 11 081 of whom were taking SU and insulin. The overall incidence of hypoglycemia (defined as first-time hospitalization; criteria were not specified) was low, occurring in 3.5% of patients over 12 years. The relative risk of having a first hypoglycemic event was 2.1 (95% CI 1.6 to 2.6) in patients taking SU and insulin compared with metformin and insulin (number needed to harm of 67).²

A retrospective study of 3192 US veterans compared insulin alone with SU and insulin. The overall incidence of hypoglycemia (defined as an emergency department visit or hospitalization) was low, with 95 events from 2001 to 2008 and no statistical difference between the groups.³

Two studies examined factors related to hypoglycemia in patients with T2DM. The first looked retrospectively at 887 182 US patients treated with any agent; 7% were taking insulin. The overall incidence of hypoglycemia (defined as hospitalization) was low, but was more frequent in patients 65 years and older compared with those younger than 65 years (0.59 vs 0.16 per 1000 patient-years). Patients aged 65 years and older had an odds ratio (OR) for hypoglycemia of 4.7 with SU and insulin compared with 4.2 for insulin alone and 3.9 for SU alone (number needed to harm of 100 000).⁴

The second looked retrospectively at 166 806 patients in Japan treated with any agent; 22% were taking insulin. The incidence of hypoglycemia (defined as an emergency department visit or hospitalization, coma, seizure, or unspecified convulsions) was 3.7 per 1000 patient-years, with the highest rate in patients 75 years and older (7.59 per 1000 patient-years). Compared with patients taking hypoglycemic agents other than SU, patients had an increased OR of hypoglycemia if they took SU and insulin (OR=18.4, 95% CI 13.1 to 25.8), insulin alone (OR=14.1, 95% CI 10.8 to 18.4), or SU alone (OR=6.3, 95% CI 4.8 to 8.2).⁵

Editor's take-away

Severe hypoglycemic events secondary to hypoglycemic agents were uncommon in randomized controlled trials and in large cohorts. These events affected patients prescribed any hypoglycemic agent but occurred slightly more often with SUs, and slightly more often in the elderly. 

Dr Kolman is Assistant Professor and Dr Freeman is Clinical Professor in the Department of Family and Community Medicine at the University of Arizona in Tucson. Dr Howe is a librarian in the Health Sciences Library at the University of Arizona.

Competing interests

None declared

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