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ORIGINAL ARTICLE

Variations in Octreotide Dosing in Published Reports of Sulfonylurea Toxicity: A Systematic Review, 1988-Present

Erin Ryan[1] · **William Rushton**[2,3]

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Abstract

Background Octreotide is commonly used to treat hypoglycemia due to sulfonylurea toxicity, but optimal dosing for this indication is not well defined.

Methods We performed a systematic review to identify cases in the medical literature of octreotide use for sulfonylurea poisoning. Literature published on octreotide and sulfonylureas between octreotide's FDA approval on 10/21/1988 and 8/15/2024 was reviewed.

Results Eighty unique patient cases (66 adults/adolescents and 14 pediatric patients) from 61 sources were included in the final analysis. These included 41 octreotide dosing strategies that differed in dose, frequency, and/or route of administration. Subcutaneous dosing, primarily within the range of 50–100 mcg per dose at a frequency of every 6–8 h, was the most common regimen in adults while intravenous dosing of 1 mcg/kg was most prevalent in pediatrics. There were no significant differences in duration of therapy or total dose of octreotide in adults with intermittent subcutaneous vs intravenous dosing. Treatment of hypoglycemia and maintenance of euglycemia was similar among all routes of administration. Infusions had similar durations but higher total doses of octreotide. Higher intermittent bolus doses were associated with shorter durations of therapy. Intentional exposures were associated with higher doses and longer duration of treatment with octreotide. Three adverse reactions to octreotide were reported. Except for 2 cases, all patients survived without any long-term complications.

Conclusion Despite widespread variation in octreotide dosing and administration, our report showed similar efficacy and safety with various octreotide dosing practices.

Keywords Octreotide · Sulfonylurea · Antidotes · Pharmacokinetics

Background

First recognized in the mid-1960s for their benefit in treating diabetes, sulfonylureas inhibit potassium efflux from pancreatic beta islet cells, inducing cellular depolarization and increasing intracellular calcium, which ultimately stimulates insulin release [1]. Over the last two decades as newer antihyperglycemic agents have proliferated, sulfonylurea use has declined. Despite this, both glipizide and glimepiride are listed in the top 100 most prescribed medications in the United States [2]. Sulfonylurea poisoning remains a common presentation in emergency departments, as evidenced by the most recent annual report from America's Poison Centers, which states that 29% of over three thousand sulfonylurea exposures were managed in healthcare facilities [3]. Notably, exposures may occur even in those who are not prescribed sulfonylureas. Multiple reports spanning from 2006–2024 have described cases in which supplements or recreational drugs were found to be adulterated with sulfonylureas [4–11].

Octreotide was first recognized as a potential therapy for refractory hypoglycemia in a 1986 Lancet report. Phillips et al. described the successful use of octreotide infusion to treat refractory hypoglycemia in a 32-year-old female

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✉ Erin Ryan
erin.ryan@bannerhealth.com

[1] Banner Poison and Drug Information Center, Banner University Medical Center Phoenix, Phoenix, AZ, USA

[2] Office of Medical Toxicology, University of Alabama Birmingham, Birmingham, USA

[3] Alabama Poison Information Center, Children's of Alabama, Birmingham, USA

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receiving quinine for malaria. Subsequently, healthy volunteers were given quinine and either an octreotide infusion or a saline solution for four hours. The group receiving octreotide showed a significant reduction in insulin release compared to the saline group [12]. As quinine enhances insulin secretion through similar mechanisms to sulfonylureas, later work built upon this finding, with Boyle et al. first demonstrating the efficacy of octreotide in sulfonylurea-induced hypoglycemia [13].

Although octreotide is not approved by the United States Food and Drug Administration (FDA) for sulfonylurea toxicity, it is widely recognized as a mainstay of treatment, particularly in cases refractory to supplemental parenteral dextrose therapy [1]. Octreotide inhibits calcium influx into pancreatic beta islet cells, reducing insulin release at a site downstream from the action of sulfonylureas [14]. Current United States antidote stocking guidelines recommend octreotide be available within 60 min in all emergency departments [15].

Despite its established role in sulfonylurea toxicity, the optimal administration and dosing of octreotide has not been definitively determined. A widely cited 2012 review summarized the pharmacology, animal data, interventional trials, and many of the case reports available at the time [1], but literature to date has not closely examined the wide heterogenicity of octreotide dosing strategies with regards to efficacy and safety. Consequently, this report aims to address the following conundrum: in patients receiving octreotide for sulfonylurea-induced hypoglycemia, how do variations in dosing regimens (dose, route, duration) impact treatment outcomes and the occurrence of adverse drug reactions?

Methods

We performed a systematic review in accordance with the PRISMA standards to identify cases in the medical literature of octreotide use for sulfonylurea poisoning in which dosing was described [16].

We searched literature published between octreotide's approval by the FDA on 10/21/1988 and 8/15/2024 using the keywords "sulfonylurea" and "octreotide" in PubMed, Embase, and CINAHL databases.

We included cases without regard to patient age or the presence of coingestants. We excluded articles that did not describe the administration of octreotide to treat sulfonylurea-induced hypoglycemia, were missing information about the dose or route of octreotide, were not published in English, did not describe human toxicity, or did not include information about individual patients and their clinical course. Using the same keywords, we searched abstracts presented at the North American Congress of Clinical Toxicology, the International Congress of the European Association of Poison Centres and Clinical Toxicologists, and the American College of Medical Toxicology Annual Scientific Meeting. We examined references from all reviewed sources for additional cases that did not return in the initial search criteria.

We reviewed cases that met the inclusion and exclusion criteria using a standardized data form. A certified specialist in poison information extracted the following variables: age, gender, history of diabetes, renal or hepatic dysfunction, circumstances of exposure (agent, dose, reason, chronicity), octreotide dose, route of administration (subcutaneous [SQ], intravenous bolus [IV], or continuous infusion), duration of octreotide treatment, patient outcome, year and country of publication, glucose concentrations (nadir and pre- and post-octreotide), concomitant therapies, and adverse events attributed to octreotide.

We assigned the following determinations a priori. We defined pediatric cases as patients 11 years old or younger, while we grouped patients 12 years and older as adolescents and adults. We separated younger patients due to pediatric dosing being predominantly weight-based, in contrast to adolescent and adult dosages [17], which challenges direct comparisons between the groups. We considered exposures chronic if they lasted more than 24 h (e.g., normal therapeutic use), acute on chronic if a single large ingestion occurred in the context of chronic use, and acute if they lasted less than 24 h. We categorized dosing as a continuous infusion if more than half of the duration of therapy involved an infusion (e.g., a bolus followed by an infusion was classified as an infusion). A blood glucose of less than 70 mg/dl constituted hypoglycemia for this study. We considered a blood glucose less than 70 mg/dl occurring one hour or more after the first dose of octreotide to be hypoglycemia post-octreotide. We defined sustained euglycemia as the point after the first dose of octreotide beyond which all reported blood glucose measurements remained greater than 70 mg/dl.

The following definitions described the etiology of sulfonylurea toxicity: therapeutic use referred to cases in which the patient took a sulfonylurea as prescribed; suicide attempt included any attempt of self-harm; exploratory usage described ingestion by a young child who gained access to the xenobiotic in their environment; therapeutic error referred to the ingestion of an incorrect dose, route, or drug (including iatrogenic errors); adulteration involved the misrepresentation of a sulfonylurea as another xenobiotic (e.g., sulfonylureas sold as recreational drugs or health supplements); and misuse indicated that the sulfonylurea was taken recreationally.

We used standard statistical methods (Microsoft Excel, Redmond, Washington) to generate descriptive statistics (counts and percentages for categorical data, medians and interquartile ranges for continuous variables). We compared

normally distributed and non-normally distributed continuous variables using a Student's t-test or Mann–Whitney U test, respectively. A Chi square or Fisher exact test compared categorical variables. We applied the Joanna Briggs Institute critical appraisal tool to assess the methodological quality and potential bias of each case report and series [18].

Results

The final analysis included 80 unique patient cases from 61 sources (Fig. 1). These encompassed 66 adult and adolescent cases and 14 pediatric cases (Table 1) representing 41 different octreotide dosing strategies (Table 2). Variations in dosing were not limited only to individual dose but also included differences in frequency or route of administration. The most implicated sulfonylureas were glyburide (29/80, 36.3%), glipizide (23/80, 28.8%), and glimepiride (15/80, 18.8%).

Adolescent and Adult Dosing

There were 66 adult and adolescent subjects with a median age of 56.5 years (range 15–89 years) of which 68.2% (n = 45) were male. Thirty-eight patients (57.6%) were known to be diabetic and 26 had renal impairment (39.4%). The most common scenario (n = 28, 42.4%) was hypoglycemia in the setting of therapeutic dosing (due to declining renal function, drug interactions, or changes to diet), followed by suicide attempts (n = 20, 30.3%) and adulterated products (n = 9, 13.6%). The adulteration cases included glyburide sold on the street as an anabolic steroid [4, 5]

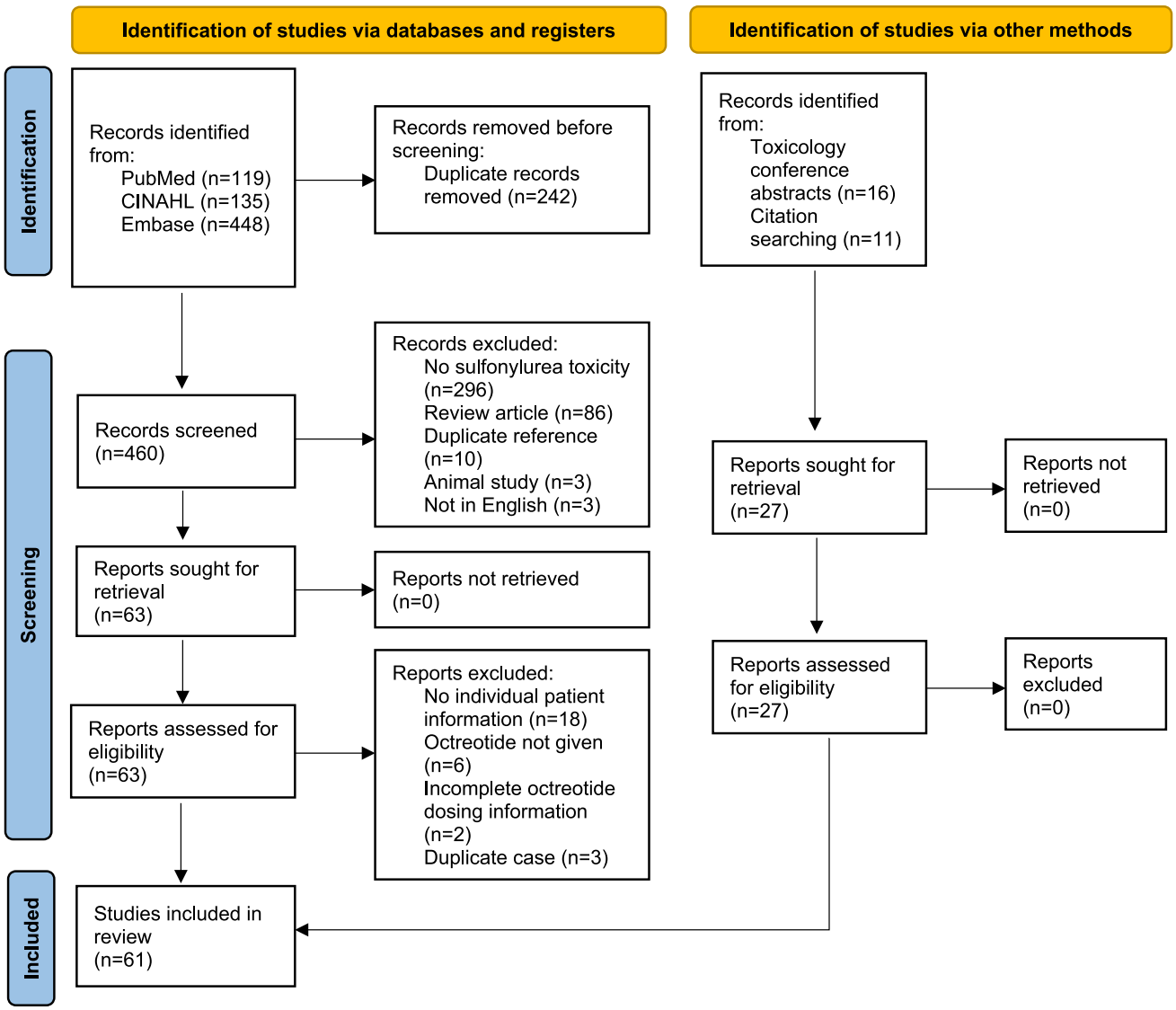

Fig. 1 PRISMA flow diagram of systematic review.

Table 1 Demographics, exposure details, and octreotide dosing of all patients (N = 80).

	Adults/Adolescents (n = 66)	**Pediatrics (n = 14)**
Age *Median (IQR) (range)*	56.5 years (40.5−68.75) (15−89)	1.96 years (1.44−2.13) (1−6)
Male *N (%)*	45 (68.2%)	11 (78.6%)
Medical History *N (%)*		
Diabetes	38 (57.6%)	0 (0%)
Renal Impairment	26 (39.4%)	0 (0%)
Hepatic Impairment	4 (6.06%)	0 (0%)
Chronicity *N (%)*		
Acute	17 (25.8%)	13 (92.9%)
Acute on chronic 8 (12.1%)	Chronic 30 (45.5%)	Unknown 11 (16.7%)
0 (0%)	1 (7.14%)	0 (0%)
Scenario *N (%)*		
Adverse effect	28 (42.4%)	0 (0%)
Suicide attempt	20 (30.3%)	0 (0%)
Exploratory	0 (0%)	13 (92.9%)
Adulteration	9 (13.6%)	0 (0%)
Therapeutic error	7 (10.6%)	1 (7.14%)
Misuse	1 (1.52%)	0 (0%)
Unknown	1 (1.52%)	0 (0%)
Sulfonylurea Agent *N (%)*		
Glyburide	24 (36.4%)	5 (35.7%)
Glipizide	16 (24.2%)	7 (50%)
Glimepiride	14 (21.2%)	1 (7.14%)
Gliclazide	8 (12.12%)	0 (0%)
Tolbutamide	2 (3.03%)	0 (0%)
Chlorpropamide	1 (1.52%)	0 (0%)
Gliquidone	1 (1.52%)	0 (0%)
Unknown	0 (0%)	1 (7.14%)
Outcome *N (%)*		
Full recovery	63 (95.5%)	13 (92.9%)
Persistent effects	0 (0%)	1 (7.14%)
Death	1 (1.52%)	0 (0%)
Unknown	2 (3.03%)	0 (0%)
Other Therapies *N (%)*		
IV dextrose (> 10%)	58 (87.9%)	9 (64.3%)
IV dextrose (≤ 10%)	39 (59.1%)	12 (85.7%)
Oral glucose/food	18 (27.3%)	2 (16.7%)
GI decontamination	11 (16.7%)	1 (7.14%)
Glucagon	11 (16.7%)	2 (16.7%)
Diazoxide	1 (1.52%)	0 (0%)
Corticosteroids	2 (3.03%)	0 (0%)
Naloxone	3 (4.92%)	0 (0%)
Potassium	1 (1.52%)	0 (0%)
Verapamil	1 (1.52%)	0 (0%)
Anticonvulsants	0 (0%)	2 (16.7%)
Time to Octreotide *Median (IQR) (range)*	8.5 h (4–14.75) (2–32)	19 h (6.5–25) (2–55)
Octreotide Route *N (%)*		

Table 1 (continued).

	Adults/Adolescents (n = 66)	Pediatrics (n = 14)
SQ	53 (80.3%)	4 (28.6%)
IV	6 (9.09%)	7 (50%)
CI	6 (9.09%)	3 (21.4%)
Combination	1 (1.52%)	0 (0%)
Single Dose Octreotide *N (%)*	18 (27.3%)	7 (50%)
Octreotide Initial Dose *Median (IQR) (range)*		
Bolus	50 mcg (50–50) (25–120)	1 mcg/kg (1–1.13) (0.9–2)
Infusion Rate	50 mcg/h (25–87.5) (25–125)	2 mcg/kg/h (1.5–3.5) (1–5)
Octreotide Initial Frequency *Median (IQR) (range)*	8 h (6–8) (4–12)	6 h (6–6) (6–8)
Octreotide Infusion Duration *Median (IQR) (range)*	9 h (8–88.5) (7–168)	39 h (25–53) (11–67)
Octreotide Total Duration *Median (IQR) (range)*	12 h (SD–20.25) (SD–168)	3.25 h (SD–13.5) (SD–85)
Total Octreotide Dose *Median (IQR) (range)*	150 mcg (100–200) (50–1175)	2 mcg/kg (1.31–3.45) (1–70)

IQR Interquartile range, *CI* continuous infusion, *IV* intravenous bolus, *SD* single dose, *SQ* subcutaneous

or as diazepam [7], contamination of an over-the-counter erectile dysfunction medication with glyburide [6], illicitly purchased oxycodone containing glipizide [11], an unapproved nutritional supplement containing unlabeled tolbutamide [10], and cases of cocaine, methamphetamine, and fentanyl cut with sulfonylureas [8, 9].

Twenty-nine unique dosing regimens were identified. The most common route of administration of octreotide was subcutaneous (SQ) (n = 53, 80.3%). Intravenous (IV) boluses and continuous infusions were both used in six patients (9.1%) each. One patient was started on SQ octreotide before inadvertently receiving one dose IV after admission to the intensive care unit; SQ dosing was resumed after the error was discovered. The authors of this case report surmised that this accidental IV dose was responsible for the recurrence of hypoglycemia two hours later although no pharmacokinetic or mechanistic explanation for this assumption was provided [4].

The number of doses given ranged from 1–21 with SQ administration and 1–13 with IV. Eighteen cases (27.3%) received only a single dose. Dosing frequency ranged from every 4–12 h with most patients (32/42, 76.2%) receiving a dose every six or eight hours. Median duration of octreotide therapy was similar for both intermittent dosing (12 h) and continuous infusion (13 h), although the overall range of durations was wide (a single dose to 168 h).

Pediatric Dosing

Fourteen pediatric patients were included in this analysis. Median age was 23.5 months (range: 12 months—6 years), 11 (78.6%) were male, and none were diabetic. Thirteen cases were exploratory ingestions with one therapeutic error in which a pharmacy dispensed the wrong drug. Twelve different dosing practices were used in these 14 cases. Contrary to the adult cases, the most common route of administration in pediatric patients was IV (n = 7, 50%), followed by SQ (n = 4, 29%), and then continuous infusion (n = 3, 21.4%) (Table 2).

Seven of the 14 pediatric cases were successfully treated with a single dose of octreotide. The most common initial bolus dose (either IV or SQ) was 1 mcg/kg. Doses ranged from 0.9–2 mcg/kg (median 1 mcg/kg). The dosing interval was six hours in all but one case in which 10 mcg (patient weight not given) was administered IV every eight hours. Median initial doses were the same among both the IV and SQ cohorts (1 mcg/kg). Among the three patients receiving continuous infusion, initial rates ranged from 1–5 mcg/kg/hr with titration up to 10 mcg/kg/hr in one instance.

Route of Administration

Both routes (IV and SQ) of intermittent octreotide administration utilized similar doses with a median of 1 mcg/kg in pediatrics and 50 mcg (SQ) and 75 mcg (IV) in adults (p = 0.194). There were no significant differences in duration of octreotide therapy, total dose in adults, rate of hypoglycemia after initiation of octreotide, change in blood glucose with therapy, or time to euglycemia between the two routes (Table 3). Total dose in pediatric patients was higher with SQ vs IV administration (mean of 3.5 mcg/kg vs 1.6 mcg/kg, p = 0.034).

When octreotide intermittent dosing (either SQ or IV) was compared to continuous infusion, there were no

Table 2 Published dosing strategies of octreotide in the treatment of sulfonylurea-induced hypoglycemia.

All Adult Dosing Strategies

SQ

Dose	**Number of Doses** *Range*	**ADRs**	**Time to Sustained BG > 70 (hours)** *Median (IQR) (range)*	**Total OCT Dose (mcg)** *Median (IQR) (range)*	**Total OCT Duration (hours)** *Median (IQR) (range)*	**References**
25 mcg × 1 → 50 mcg q12h	3	none	NR	125	24	Vallurupalli 2010 [34]
30 mcg q6h	NR	none	NR	NR	NR	Zafar 2021 [35]
40 mcg q12h	2	none	NR	80	12	McLaughlin 2000 [36]
50 mcg × 1	1	none	1 h (1–4) (0.33–16)	50	SD	Hung 1997 [22], McLaughlin 2000 [36], Crawford 2004 [37], Yavari 2007 [38], Gul 2008 [31], Brenner 2009 [5], Hanchard 2009 [39], Cussen 2019 [40], Warpinski 2022 [9], Banerjee 2023 [41]
50 mcg q6h	2–21	hyperkalemia [21]	2 (2–2) (2–2)	200 (150–350) (100–1050)	18 (12–36) (6–120)	Gonzalez 2007 [42], Chan 2009 [6], Adabala 2010 [21], Cabot 2015 [43], Kim 2019 [44], Sultani 2023 [10]
50 mcg q8h	2–7	none	4.5 (2–8) (1–24)	150 (125–175) (100–350)	16 (12–20) (8–48)	McLaughlin 2000 [36], Carr 2002 (2) [45], Chinnappa 2003 (2) [46], Fleseriu 2006 (6) [47], Zaid 2015 [48], Nakaya 2019 [49], Khan 2019 [50], Braet 2020 [51], Gothong 2022 [8]
50 mcg q12h	2–3	none	5.5 (3.25–7.75) (1–10)	100 (100–112.5) (100–150)	12 (12–15) (12–24)	Krentz 1993 [26], McLaughlin 2000 [36], Nzerue 2003 [52], Vallurupalli 2010 [34]
50 mcg q12h × 1 → 50 mcg q6h × 5	6	none	NR	300	36	Igala 2014 [53]
50 mcg × 1 → 100 mcg q6h × 1 → 100 mcg q12h × 2	4	none	NR	350	30	Graudins 1997 [54]
75 mcg × 1	1	none	1	75	SD	Yamaguchi 2015 [55]
75 mcg q6h	2	none	NR	150	6	Gunaratne 2018 [56]
100 mcg × 1	1	none	2 (1.5–2) (1–2)	100	SD	Braatvedt 1997 [57], McLaughlin 2000 [36], Lung 2012 [7], Kothari 2021 [58], Savarino 2024 [11]
100 mcg q6h	2	none	NR	200	6	Khan 2022 [59]

Table 2 (continued).

All Adult Dosing Strategies						
100 mcg q6h × 3 → 100 mcg q13h × 1	4	none	NR	400	19	McLaughlin 2000 [36]
100 mcg q8h × 1 → 50 mcg q8h × 3	4	none	NR	250	24	McLaughlin 2000 [36]
120 mcg × 1 → 50 mcg q6h	NR	none	1	NR	NR	Ausman 2021 [60]
IV						
Dose	**Number of Doses** *Range*	**ADRs**	**Time to Sustained BG > 70 (hours)** *Median (IQR) (range)*	**Total OCT Dose (mcg/kg)** *Median (IQR) (range)*	**Total OCT Duration (hours)** *Median (IQR) (range)*	**References**
50 mcg × 1	1	none	3	50	SD	Sayed 2023 [61]
50 mcg q4h	13	none	1	650	48	Barkin 2013 [62]
50 mcg × 1 → 100 mcg q6h	6	none	13	550	30	Lung 2012 [7]
100 mcg × 1	1	none	3	100	SD	Abdullah 2023 [63]
100 mcg q6h	2	bradycardia and respiratory distress [20]	NR	200	6	Chew 2008 [20]
100 mcg q9h	2	none	10	200	9	Green 2003 [64]
Combination (SQ and IV)						
Dose	**Number of Doses** *Range*	**ADRs**	**Time to Sustained BG > 70 (hours)** *Median (IQR) (range)*	**Total OCT Dose (mcg)** *Median (IQR) (range)*	**Total OCT Duration (hours)** *Median (IQR) (range)*	**References**
50 mcg SQ × 1 → 50 mcg IV q6h × 1 → 50 mcg SQ q6h	12	none	NR	250	24	Kalman 2006 [4]
Continuous Infusion						
Dose	**Infusion Duration (hours)** *Range*	**ADRs**	**Time to Sustained BG > 70 (hours)** *Median (IQR) (range)*	**Total OCT Dose (mcg)** *Median (IQR) (range)*	**Total OCT Duration (hours)** *Median (IQR) (range)*	**References**
1.8 mcg/kg/h	13	none	1	NR	13	Crawford 2004 [65]
50 mcg SQ → 25 mcg/h	NR	none	NR	NR	NR	Soderstrom 2006 [33]
100 mcg IV → 50 mcg/h	7	none	2	450	7	Covvey 2010 [66]
50 mcg/h → 100 mcg/h → NR mcg/h	168	none	NR	NR	168	Bui 2000 [67]
50 mcg SQ → 125 mcg/h	9	none	NR	1175	9	McLaughlin 2000 [36]
50 mcg SQ q6h → continuous infusion (initial rate 25 mcg/h, titrated based on BG)	NR	none	NR	NR	NR	Yanta 2012 [68]

Table 2 (continued).

All Adult Dosing Strategies

All Pediatric Dosing Strategies

SQ

Dose	**Number of Doses** *Range*	**ADRs**	**Time to Sustained BG > 70 (hours)** *Median (IQR) (range)*	**Total OCT Dose (mcg/kg)** *Median (IQR) (range)*	**Total OCT Duration (hours)** *Median (IQR) (range)*	**References**
0.9 mcg/kg q6h × 3 → 0.9 mcg/kg q12h × 1	4	none	19	3.6	24	Pelavin 2009 [69]
1 mcg/kg q6h × 2 → 1.25 mcg/kg q6h × 1 → 1.5 mcg/kg q6h × 1	4	none	15	4.75	18	Lugassy 2009 [70]
2 mcg/kg × 1	1	none	2	2	SD	Glatstein 2010 [71]
10 mcg × 1	1	none	NR	NR	SD	Muller 2003 [72]

IV

Dose	**Number of Doses** *Range*	**ADRs**	**Time to Sustained BG > 70 (hours)** *Median (IQR) (range)*	**Total OCT Dose (mcg/kg)** *Median (IQR) (range)*	**Total OCT Duration (hours)** *Median (IQR) (range)*	**References**
1 mcg/kg × 1	1	rash [19]	1	1	SD	Tenenbein 2006 [19], Blume-Odom 2010 [73]
1 mcg/kg q6h	2–3	none	3	2.5 (2.25–2.75) (2–3)	9 (7.5–10.5) (6–12)	Glatstein 2010 [71], Kumar 2017 [74]
1.25 mcg/kg × 1	1	none	3	1.25	SD	Mordel 1998 [75]
1.5 mcg/kg × 1	1	none	NR	1.5	SD	Calello 2006 [76]
10 mcg q8h	2	none	1	NR	8	Kent 2003 [77]

Continuous Infusion

Dose	**Infusion Duration (hours)** *Range*	**ADRs**	**Time to Sustained BG > 70 (hours)** *Median (IQR) (range)*	**Total OCT Dose (mcg/kg)** *Median (IQR) (range)*	**Total OCT Duration (hours)** *Median (IQR) (range)*	**References**
2 mcg/kg IV → 2 mcg/kg/h	1	none	2	NR	NR	Rath 2008 [78]
1 mcg/kg q6h × 3 → 1 mcg/kg/h	85	none	19	70	85	Llamado 2013 [23]
1 mcg/kg SQ × 1 → 5 mcg/kg/h (titrated to 10 mcg/kg/h)	11	none	NR	99.5	NR	Escajeda 2013 [79]

ADR adverse drug reaction, *BG* blood glucose, *IV* intravenous bolus, *NR* not reported, *OCT* octreotide, *SD* single dose, *SQ* subcutaneous

significant differences in hypoglycemia, change in blood glucose, or time to euglycemia. Duration of octreotide therapy was also similar between the two cohorts. However, total doses in adult patients were significantly higher (median 812.5 mcg, IQR 631.2–993.8 mcg) with continuous infusions compared to intermittent bolus dosing (median 137.5 mcg, IQR 100–200 mcg) (p = 0.026).

Dose and Frequency

Median dosing intervals were similar between IV (6 h, IQR 6–7 h) and SQ (8 h, IQR 6–8 h) intermittent administration. When cases with short dosing intervals (4–6 h) were compared to long dosing intervals (8–12 h), no difference was found in duration of octreotide, rates of hypoglycemia, or time to euglycemia, but short dosing intervals were associated with higher total doses (median 200 mcg, IQR 175–450 mcg vs median 150 mcg, IQR 100–200 mcg, p = 0.010) (Table 3). Intermittent doses in adults ranged from 25 to 120 mcg, but 54/60 (90%) fell within the range of 50–100 mcg. Low dose (25–50 mcg) octreotide compared to high dose (75–100 mcg) did not show a significant difference in incidence of hypoglycemia or time to euglycemia (Table 3). While total octreotide dose was similar between low and high dose patients, duration of therapy was significantly shorter with high dose (median single dose, IQR single dose-6 h) vs low dose (median 12 h, IQR single dose-24 h) (p = 0.009).

Geographic and Temporal Variation

Patterns of routes of octreotide administration over four decades are presented in Fig. 2. Continuous infusions were first reported in the 2000s, with all cases published in the 1990s administering octreotide via IV or SQ boluses. While a variety of routes of administration were reported, subcutaneous injection remained the most common in each decade. The incidence of different routes did not differ statistically by decade (p = 0.810). Median single and total doses also remained similar across decades.

Further trends in octreotide practice patterns were identified when cases were sorted by region. Prevalent routes differed between continents with 100% of cases in Europe using subcutaneous administration, a variety of routes in North America (71.2% SQ, 17.0% IV, 6% infusion, 1.69% combination) and in Asia (66.7% SQ, 33.3% IV), and a predominance of infusions in Oceania (40% SQ, 60% infusion) (p = 0.047).

Intentional vs Accidental Exposures

Among adult and adolescent patient cases, intentional exposures (suicide attempts or misuse) were associated with higher total doses of octreotide (median 200 mcg, IQR 137.5–262.5 mcg) than accidental exposures (therapeutic errors or adverse effects) (median 100 mcg, IQR 93.8–150 mcg) (p = 0.022) (Table 4). Duration of octreotide therapy was also longer in intentional vs accidental adult/adolescent ingestions (median 16 h, IQR 9–24 h vs median 8 h, IQR single dose – 16 h, p = 0.026). There were no differences between intentional and accidental ingestions in incidence of post-octreotide hypoglycemia, change in blood glucose, or time to sustained euglycemia.

Safety and Patient Outcomes

Adverse reactions to octreotide were reported in three cases. These included a rash in a 2-year-old male that developed immediately after an initial 1 mcg/kg IV dose [19], a 26-year-old female with bradycardia and respiratory distress that resolved without intervention after her second 100 mcg IV dose [20], and a 48-year-old male with dialysis-dependent end stage renal disease who developed hyperkalemia requiring medical intervention after his third 50 mcg SQ dose [21].

Outcomes overall were positive with only one death and one case of persistent morbidity. Hung et al. reported a 52-year-old male who intentionally ingested 60 chlorpropamide tablets and arrived at the emergency department unresponsive. He was given five boluses of dextrose before SQ octreotide was initiated three hours after admission with subsequent normalization of his serum glucose. Despite these efforts, he remained in a persistent vegetive state and died on hospital day five when care was withdrawn [22]. Llamado et al. described a 17-month-old who presented with severe hypoglycemia, cerebral edema, and seizures after an exploratory ingestion of glipizide. He was treated with IV dextrose and three doses of SQ octreotide (1 mcg/kg) before being transitioned to a continuous infusion of octreotide (1 mcg/kg/h) for 67 h along with escalating dextrose requirements and 3% sodium chloride. At discharge CT imaging reported resolution of cerebral edema and minor persisting abnormalities in his neurologic exam, although it is unclear whether these were permanent [23].

Methodological Quality

The bias assessment for the included case reports and case series is provided in supplemental Table 1. Of the 53 case reports, 34 (64%) lacked clear documentation in at least one of the eight assessed domains, with the most common omissions being the patient's full history or demographics (n = 15). The eight included case series varied in quality, with six failing to explicitly use complete or consecutive patient inclusion criteria. However, all case series reported clear outcomes for all included patients.

Table 3 Statistical comparisons of dosing strategies.

	SQ (n = 57)	IV (n = 13)	p-value	Bolus (SQ or IV) (n = 71)	CI (n = 9)	p-value	High Dose Bolus (n = 12)	Low Dose Bolus (n = 43)	p-value	Short Interval (n = 17)	Long Interval (n = 26)	p-value
Duration of OCT *Median (IQR)*	12 h (SD–18)	6 h (SD–9)	0.225	8 h (SD–18)	13 h (9–85)	0.125	SD (SD-6)	12 h (SD–24)	**0.009**	15 h (6–28.5)	15 h (12–24)	0.907
OCT Total Dose (adults) *Median (IQR)*	100 mcg (100–200)	200 mcg (125–462.5)	0.187	137.5 mcg (100–200)	812.5 mcg (631.25–993.75)	**0.026**	100 mcg (100–200)	112.5 mcg (50–162.5)	0.574	200 mcg (175–450)	150 mcg (100–200)	**0.010**
OCT Total Dose (peds) *Mean (std dev)*	3.45 mcg/kg (1.38)	1.63 mcg/kg (0.77)	**0.034**	2.23 mcg/kg (1.3)	ID	–	–	–	–	3.25 mcg/kg (1.39)	ID	–
BG < 70 Post-OCT *N (%)*	18/51 (35.3%)	2/11 (18.2%)	0.478	21/63 (33.3%)	4/8 (50%)	0.440	3/10 (30%)	15/38 (39.5%)	0.722	7/13 (53.8%)	9/25 (36%)	0.323
ΔBG Post-OCT *Mean (std dev)*	56.03 mg/dl (57.65)	69.4 mg/dl (75.06)	0.657	58.34 mg/dl (59.67)	82 mg/dl (176.78)	0.881	52.6 mg/dl (26.86)	61.89 mg/dl (62.55)	0.731	–	–	–
Time from OCT to Sustained Euglycemia *Median (IQR)*	2 h (1–8)	3 h (1–3)	1.000	2 h (1–8)	2 h (1.75–6.25)	1.000	2 h (1.25–2.75)	2.5 h (1–7.25)	0.677	2.5 h (1.25–10.5)	4.5 h (1.25–9.5)	0.841
Sustained Euglycemia Within 4 Hours *N (%)*	19/29 (65.5%)	7/9 (77.8%)	0.689	26/38 (68.4%)	3/4 (75%)	1.000	5/6 (83.3%)	15/23 (65.2%)	0.633	–	–	–

BG blood glucose, *IQR* Interquartile range, *CI* continuous infusion, *high dose* 75–100 mcg, *ID* insufficient data, *IV* intravenous bolus, *long interval* q8-12 h, *low dose* 25–50 mcg, *OCT* octreotide, *peds* pediatric patients, *SD* single dose, *short interval* q4-6 h, *SQ* subcutaneous, *std dev* standard deviation

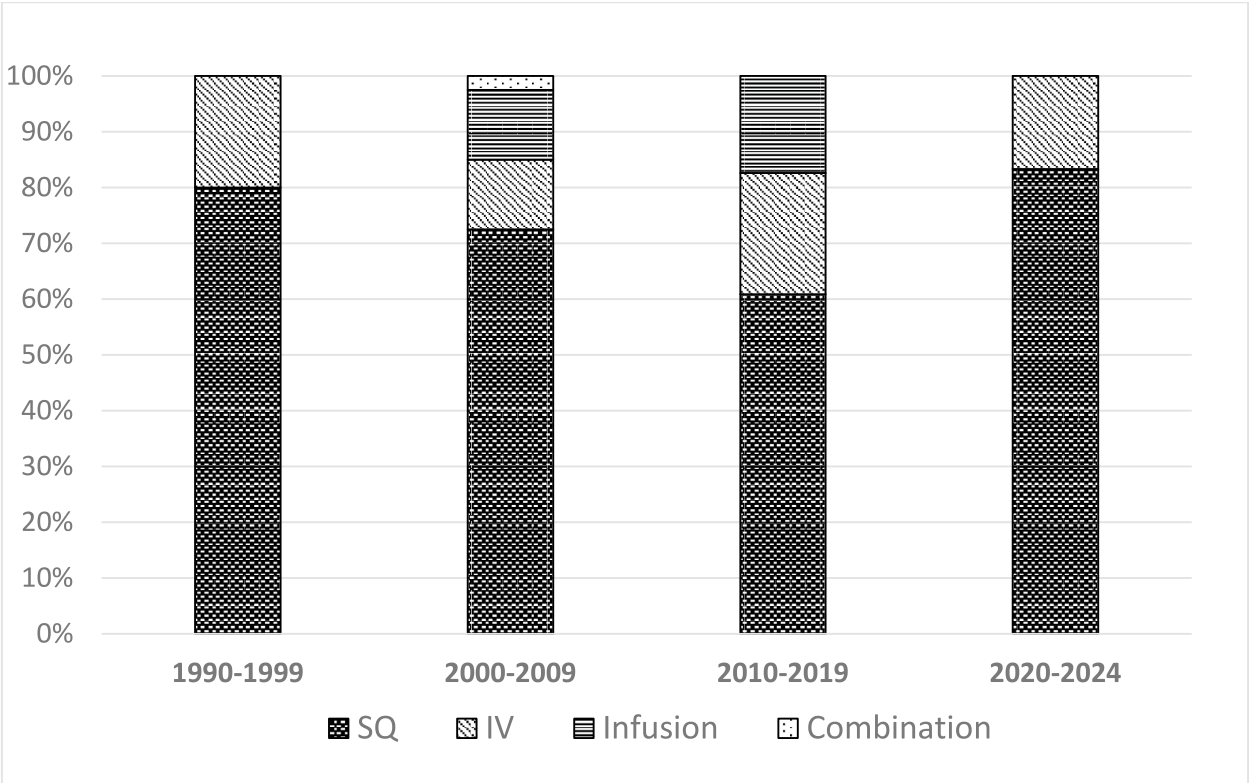

Fig. 2 Route of octreotide administration by decade (p = 0.810).

Discussion

These findings highlight the significant variation in practice in how octreotide is given for the treatment of sulfonylurea-induced hypoglycemia. Goldfrank's Toxicologic Emergencies states that for adults "a dose of 50 mcg octreotide SC given every 6 h is recommended for a total duration of 24 h," however it is unclear why this route, dose, frequency, or duration is recommended over others [17]. Other references are less prescriptive, quoting a dose of 50–100 mcg given either SQ or IV every six to 12 h [24]. Many of the case reports included in this analysis acknowledge a lack of standardized dosing, stating that the ideal octreotide regimen is unknown.

This heterogeneity of dosing strategies was apparent even in the earliest use of octreotide for sulfonylurea toxicity.

Table 4 Statistical comparison of intentional (includes suicide attempts and misuse) vs accidental (includes therapeutic errors and adverse effects) in adolescent and adult patients. Pediatric cases, unknown scenarios, and adulteration cases are excluded.

	Intentional (n = 21)	Accidental (n = 35)	p-value
Duration of OCT *Median (IQR)*	16 h (9−24)	8 h (SD−16)	**0.026**
OCT Total Dose *Median (IQR)*	200 mcg (137.5−262.5)	100 mcg (93.75−150)	**0.022**
BG < 70 Post-OCT *N (%)*	7/17 (41.2%)	9/31 (29.0%)	0.524
ΔBG Post-OCT *Mean (std dev)*	87.8 mg/dl (36.93)	51.67 mg/dl (64.56)	0.247
Time from OCT to Sustained Euglycemia *Median (IQR)*	3 h (1−11.75)	2 h (1−4)	0.383
Sustained Euglycemia Within 4 Hours *N (%)*	5/8 (62.5%)	17/21 (81.0%)	0.357

BG blood glucose, *IQR* interquartile range, *OCT* octreotide, *SD* single dose, *std dev* standard deviation

Boyle et al. showed that octreotide was effective for this purpose in 1993 when they administered a 30 ng/kg/min continuous infusion to eight healthy volunteers who had been given glipizide [13]. In a subsequent report, the authors elaborated on the origins of this dose. Initially, 60 ng/kg/min was chosen to be equimolar to the established infusion rate of somatostatin (250 mcg/h) in a 70 kg individual. Due to high rates of gastrointestinal adverse effects, the infusion was later halved to 30 ng/kg/min with similar efficacy [25]. However, when a patient presented to the emergency department with significant hypoglycemia from tolbutamide toxicity, the same authors elected to treat with 50 mcg SQ octreotide every eight hours for three doses without clear explanation of why they deviated from their prior study protocol [26]. Neither of these doses are consistent with the prior reported use of octreotide for xenobiotic-induced hyperinsulinemia: a 1986 report of a 50 mcg/h infusion of octreotide used for hypoglycemia secondary to quinine [12].

The only randomized controlled trial of octreotide for sulfonylurea induced hypoglycemia came in 2008 when Fasano et al. reported on 40 patients with hypoglycemia secondary to sulfonylureas who were assigned to treatment with dextrose and either placebo or a single dose of octreotide 75 mcg SQ. Improvement in glucose homeostasis was reported in the octreotide arm but there was no discussion as to why this dose or route was chosen [27]. Despite this being the primary prospective comparative study establishing the efficacy of octreotide for sulfonylurea poisoning, 75 mcg doses are rarely reported (only two of 80 cases in this review). This may be for practical reasons: octreotide is manufactured as vials of 50, 100, 200, 500, or 1000 mcg, making dosing in multiples of 50 mcg advantageous both for convenience and to minimize drug waste [24].

Despite the variety of octreotide dosing strategies outlined in this review, few significant differences in outcomes were observed between groups. However, one notable result revealed that an initial high dose of octreotide (> 50 mcg) was associated with patients receiving only a single dose. This raises the possibility that a 50 mcg starting dose may be suboptimal in certain cases and necessitate the need for repeat doses. Supporting this hypothesis, previous pharmacokinetic studies in healthy volunteers have shown that a 50 mcg subcutaneous dose results in a peak concentration of 2.4 ng/ml ± 0.8, while a 100 mcg dose reaches a maximum concentration of 4.4 ng/ml ± 1.5 [28]. This increased octreotide concentration may enhance its ability to suppress insulin release as somatostatin type 2 receptors (SSTR2) are not fully saturated until octreotide concentrations reach approximately 10 ng/ml [29]. While this 10 ng/ml figure comes from literature on neuroendocrine tumors rather than sulfonylurea toxicity, SSTR2 is the primary somatostatin receptor subtype involved in regulation of insulin secretion by the pancreatic beta cells [1]. Further research is needed to determine the degree of SSTR2 saturation associated with maximal suppression of insulin release.

While there are no human studies comparing different dose responses of octreotide, one animal study did attempt to evaluate such a relationship. Groups of ten rabbits were all given 100 mg gliclazide orally then treated with either 50% dextrose alone or 50% dextrose plus one of three doses (25 mcg, 50 mcg, or 100 mcg SQ) of octreotide. The rabbits receiving 50 mcg or 100 mcg doses of octreotide experienced fewer hypoglycemic episodes than controls, but there was no difference between the 25 mcg group and the control group. Although the authors conclude by recommending a 100 mcg SQ dose of octreotide, extrapolation of this study to humans is limited given body mass differences between 2.5–3 kg rabbits and an average sized human [30].

The optimal dose of octreotide may also depend on severity of the exposure. Adult patients with intentional exposures received on average more total octreotide and a longer duration of octreotide therapy than accidental exposures. We suspect that this is likely related to the sulfonylurea dose as intentional ingestions are likely to involve large doses while accidental ingestions in adults are generally either therapeutic or slightly supratherapeutic doses. Not all large intentional ingestions appear to require intensive octreotide dosing, however, as single doses of 50 mcg achieved sustained euglycemia after suicidal ingestions of 250 mg of glyburide and 2400 mg of gliclazide [22, 31].

We suspect the wide variation in octreotide administration can be attributed to its diverse range of indications, each with its own recommended dosing. Previous reports have detailed different octreotide regimens for various conditions: 50–100 mcg every eight hours for up to 27 months for acromegaly, 100–1500 mcg/day for up to 16 months for thyrotropin-induced hyperthyroidism, 100–600 mcg/day for 18 months for carcinoid syndrome, and 50–1500 mcg/day for up to 38 months for diarrhea caused by tumors releasing vasoactive intestinal peptides [32].Due to the extended treatment duration in some of these other indications, the SQ route is preferred as it allows patients to self-administer. Both SQ and IV administrations show similar pharmacokinetics, with maximal absorption occurring within minutes in healthy adults, and comparable half-lives. However, the IV route can achieve significantly higher initial concentrations with less interindividual variability in the area under the curve (AUC) [28, 32] and also avoids the possibility of inadequate absorption in critically ill patients with impaired perfusion.

SQ injection was the most common route (71.3%) of administration in the cases reviewed. It is not clear why this has become the standard for administration of the drug in the setting of sulfonylurea toxicity where ability to self-administer the medication is not a consideration. In cases where patients do not have IV access at the time of administration,

the SQ route allows for rapid treatment of the hypoglycemia. However, due to the need for parenteral dextrose, most of the patients reviewed did have IV access that could be used to administer octreotide avoiding any theoretical disadvantages in SQ pharmacokinetics and painful additional injections. The tendency towards SQ dosing may simply be due to the description of this route in the early literature, an administration choice which has been perpetuated despite numerous examples of successful treatment via the IV route in subsequent publications.

Octreotide is commonly used as a continuous infusion for other indications such as variceal hemorrhage, but this route is less frequently mentioned for sulfonylurea-induced hypoglycemia. The benefits of continuous IV administration were promoted in one case where a 17-month old male developed cerebral edema after an ingestion of glipizide, leading the treatment team to switch from SQ dosing to a 1 mcg/kg/h infusion to avoid both hypo- and hyperglycemia and to limit fluid shifts [23]. Continuous octreotide infusion appears to be especially common in Australia. The authors of one Australian case report state that in their experience the commonly reported doses of 50–100 mcg IV or SQ every 6 h may be inadequate to control insulin and that they therefore recommend an initial 50 mcg IV bolus followed by an infusion at 35–50 mcg/h [33].

Despite the variability in dosing and administration, patient outcomes are generally excellent, with only one reported case of death and one persistent neurological disability. Adverse effects were exceedingly rare and predominately mild in these case reports. The three cases that did note adverse reactions did not involve excessive dosing relative to other cases. As noted previously, octreotide is safely given in much higher doses and for weeks or months at a time in other indications.

Publication bias is a major limitation of this analysis of case reports and case series. Unusual presentations of sulfonylurea exposure and doses or routes of administration of octreotide may be overrepresented due to these being considered more relevant for publication. Similarly, the considerable number of adulteration cases is likely a consequence of publication bias. Excluding publications written in languages other than English naturally biases results towards the practice patterns of English-speaking countries. A single reviewer extracted data and no kappa analysis could be performed. Comparisons did not account for differences in severity of presentation which may have influenced choice of dose. Consequently, our analysis cannot definitively determine the superiority of one dosing regimen or route over another. These results are intended primarily to highlight the diverse practices that are reported with seemingly similar efficacy and safety. Unless prospective trials determine an optimal dosing strategy, clinicians treating this condition should consider selecting a route and dose based on individual patient factors.

Conclusion

Despite three decades of use, optimal dosing and administration of octreotide for the treatment of sulfonylurea-induced hypoglycemia is not well established, with significant practice variation. Rigorous comparative studies are needed to determine whether one route, frequency, or dose is superior to another.

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Declarations

Conflicts of interest The authors report no conflicts of interest in the creation of this manuscript.

References

1. Glatstein M, Scolnik D, Bentur Y. Octreotide for the treatment of sulfonylurea poisoning. Clin Toxicol. 2012;50(9):795–804. https://doi.org/10.3109/15563650.2012.734626.
2. Kane SP. ClinCalc DrugStats Database, Version 2024.08. ClinCalc. Updated August 7, 2024. Available from: https://clincalc.com/Drugstats. Accessed November 16, 2024.
3. Gummin DD, Mowry JB, Beuhler MC, Spyker DA, et al. 2022 annual report of the national poison data system® (NPDS) from America's poison centers®: 40th Annual Report. Clin Toxicol. 2023;61(10):717–939. https://doi.org/10.1080/15563650.2023.2268981.
4. Kalman S, Rogers R, Barrueto F. Glyburide sold as "street steroid" causes hypoglycemia complicated by inappropriate IV administration of octreotide. In: Abstracts of the 2006 North American Congress of Clinical Toxicology Annual Meeting. Clin Toxicol. 2006;44(5):625–783. https://doi.org/10.1080/15563650600795966.
5. Brenner S, Halcomb S. Severe hypoglycemia after use of oxandrolone adulterated with glyburide. In: Abstracts of the XXIX International Congress of the European Association of Poison Centres and Clinical Toxicologists, May 12–15, 2009, Stockholm, Sweden. Clin Toxicol. 2009;47(5):436–510. https://doi.org/10.1080/15563650902952273.26.
6. Chan C, Tse M. A case of refractory hypoglycemia after consumption of erectile dysfunction drug adulterated with glibenclamide. In: Abstracts of the XXIX International Congress of the European Association of Poison Centres and Clinical Toxicologists, May 12–15, 2009, Stockholm, Sweden. Clin Toxicol. 2009;47(5):436–510. https://doi.org/10.1080/15563650902952273.26.
7. Lung DD, Gerona RR, Wu AHB, Smollin CG. Confirmed glyburide poisoning from ingestion of "street Valium." J Emerg Med.

2012;43(2):276–8. https://doi.org/10.1016/j.jemermed.2011.06.019.
8. Gothong C, Whitlatch HB. PSUN253 cocaine use resulting in inadvertent sulfonylurea overdose. J Endocr Soc. 2022;6:A392–3. https://doi.org/10.1210/jendso/bvac150.817.
9. Warpinski G, Spyres M. Hypoglycemia following recreational drug use. In: North American Congress of Clinical Toxicology (NACCT) 2022. Clin Toxicol. 2022;60:1–162. https://doi.org/10.1080/15563650.2022.2107776.
10. Sultani S, Cohen N, Fischer M. Old, but not outdated: tolbutamide-induced refractory hypoglycemia. IMAJ. 2023;25(5):355–6.
11. Savarino JR, Mokszycki R, Tubbs R, Wightman RS. Refractory hypoglycemia due to sulfonylurea contamination of illicit opioid medications. R I Med J (2013). 2024;107(5):11–13.
12. Phillips RE, Warrell DA, Looareesuwan S, Turner RC, et al. Effectiveness of SMS 201–995, a synthetic, long-acting somatostatin analogue, in treatment of quinine-induced hyperinsulinaemia. Lancet. 1986;1(8483):713–6. https://doi.org/10.1016/s0140-6736(86)91103-7.
13. Boyle PJ, Justice K, Krentz AJ, Nagy RJ, Schade DS. Octreotide reverses hyperinsulinemia and prevents hypoglycemia induced by sulfonylurea overdoses. J Clin Endocrinol Metab. 1993;76(3):752–6. https://doi.org/10.1210/jcem.76.3.8445035.
14. Katz MD, Erstad BL. Octreotide, a new somatostatin analogue. Clin Pharm. 1989;8(4):255–73.
15. Dart RC, Goldfrank LR, Erstad BL, Huang DT, et al. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. Ann Emerg Med. 2018;71(3):314–325.e1. https://doi.org/10.1016/j.annemergmed.2017.05.021.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
17. Smith S, Howland M. Octreotide. In: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS, editors. Goldfrank's Toxicologic Emergencies, 11e. McGraw-Hill Education; 2019.
18. Moola S, Munn Z, Tufanaru C, Aromataris E, et al. Chapter 7: systematic reviews of etiology and risk. In: Aromataris E, Munn Z (eds). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, 2017.
19 Tenenbein M. Anaphylactoid reaction to octreotide. In: Abstracts of the 2006 North American Congress of Clinical Toxicology Annual Meeting. Clin Toxicol. 2006;44(5):625–783. https://doi.org/10.1080/15563650600795966.
20 Chew T, Aks S, Mottram A, Donahue B. Octreotide-induced bradycardia in the treatment of hypoglycemia due to oral sulfonylurea overdose. In: Abstracts of the 2008 North American Congress of Clinical Toxicology Annual Meeting, Toronto. Canada Clin Toxicol. 2008;46(7):591–645. https://doi.org/10.1080/15563650802255033.
21. Adabala M, Jhaveri KD, Gitman M. Severe hyperkalemia resulting from octreotide use in a hemodialysis patient. Nephrol Dial Transplant. 2010;25(10):3439–42. https://doi.org/10.1093/ndt/gfq381.
22. Hung O, Eng J, Ho J, Aks S, Howland M, Erickson T, Hoffman R. Octreotide as an antidote for refractory sulfonylurea hypoglycemia. In: 1997 North American Congress of Clinical Toxicology annual meeting. St. Louis, Missouri, September 11–16, 1997. Abstracts. J Toxicol Clin Toxicol. 1997;35(5):467–75.
23. Llamado R, Czaja A, Stence N, Davidson J. Continuous octreotide infusion for sulfonylurea-induced hypoglycemia in a toddler. J Emerg Med. 2013;45(6):e209–13. https://doi.org/10.1016/j.jemermed.2013.05.016.
24. Dougherty PP, Klein-Schwartz W. Octreotide's role in the management of sulfonylurea-induced hypoglycemia. J Med Toxicol. 2010;6(2):199–206. https://doi.org/10.1007/s13181-010-0064-z.
25. Krentz AJ, Boyle PJ, Macdonald LM, Schade DS. Octreotide: a long-acting inhibitor of endogenous hormone secretion for human metabolic investigations. Metabolism. 1994;43(1):24–31. https://doi.org/10.1016/0026-0495(94)90153-8.
26. Krentz AJ, Boyle PJ, Justice KM, Wright AD, Schade DS. Successful treatment of severe refractory sulfonylurea-induced hypoglycemia with octreotide. Diabetes Care. 1993;16(1):184–6. https://doi.org/10.2337/diacare.16.1.184.
27. Fasano CJ, O'Malley G, Dominici P, Aguilera E, Latta DR. Comparison of octreotide and standard therapy versus standard therapy alone for the treatment of sulfonylurea-induced hypoglycemia. Ann Emerg Med. 2008;51(4):400–6. https://doi.org/10.1016/j.annemergmed.2007.06.493.
28. Kutz K, Nüesch E, Rosenthaler J. Pharmacokinetics of SMS 201–995 in healthy subjects. Scand J Gastroenterol Suppl. 1986;119:65–72. https://doi.org/10.3109/00365528609087433.
29. Woltering EA, Mamikunian PM, Zietz S, Krutzik SR, et al. Effect of octreotide LAR dose and weight on octreotide blood levels in patients with neuroendocrine tumors. Pancreas. 2005;31(4):392–400. https://doi.org/10.1097/01.mpa.0000186249.89081.0d.
30. Gül M, Cander B, Girisgin S, Ayan M, Kocak S, Unlu A. The effectiveness of various doses of octreotide for sulfonylurea-induced hypoglycemia after overdose. Adv Ther. 2006;23(6):878–84. https://doi.org/10.1007/BF02850209.
31. Gül M, Cander B, Ak A, Gïrïşgïn AS, Bayir A, Koçak S. Successful treatment of prolonged sulfonylurea-induced hypoglycemia with octreotide in a patient with chronic renal failure: case report. Turkiye Klinikleri J Med Sci. 2008;28(1):100–3.
32. Battershill PE, Clissold SP. Octreotide: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in conditions associated with excessive peptide secretion. Drugs. 1989;38(5):658–702. https://doi.org/10.2165/00003495-198938050-00002.
33. Soderstrom J, Murray L, Daly FF, Little M. Toxicology case of the month: oral hypoglycaemic overdose. Emerg Med J. 2006;23(7):565–7. https://doi.org/10.1136/emj.2006.034868.
34. Safety of subcutaneous octreotide in patients with sulfonylurea-induced hypoglycemia and congestive heart failure. Ann Pharmacother. 2010;44(2):387–90. https://doi.org/10.1345/aph.1M433.
35. Zafar S, Mahali LP, Ahsan H. Role of octreotide in sulfonylurea-induced hypoglycemia. J Endocr Soc. 2021;5(Suppl_1):A396–7. https://doi.org/10.1210/jendso/bvab048.807.
36. McLaughlin SA, Crandall CS, McKinney PE. Octreotide: an antidote for sulfonylurea-induced hypoglycemia. Ann Emerg Med. 2000;36(2):133–8. https://doi.org/10.1067/mem.2000.108183.
37. Crawford B, Perera C. Octreotide treatment for sulfonylurea-induced hypoglycemia. Med J Aust. 2004;180(10):540–1. https://doi.org/10.5694/j.1326-5377.2004.tb06064.x.
38. Yavari A, Ostermann M, MacLean D, Scoble J. Octreotide for relapsing sulfonylurea-induced hypoglycemia in a dialysis patient. Dial Transplant. 2007;36(4):221–6. https://doi.org/10.1002/dat.20121.
39. Hanchard B, Boulouffe C, Vanpee D. Sulfonylurea-induced hypoglycemia: use of octreotide. Acta Clin Belg. 2009;64(1):56–8. https://doi.org/10.1179/acb.2009.010.
40. Cussen L, Pazderska A, Healy M. The use of octreotide in the management of sulfonylurea-induced hypoglycemia. In: Irish Endocrine Society 43rd Annual Meeting. Ir J Med Sci. 2019;188(Suppl 9):201–53. https://doi.org/10.1007/s11845-019-02073-w.
41. Banerjee A, Kyaw MW. Severe hypoglycaemia in an elderly patient with Alzheimer's dementia and type 2 diabetes mellitus: a case report. Cureus. 2023;15(11):e49423. https://doi.org/10.7759/cureus.49423.
42. Gonzalez RR, Zweig S, Rao J, Block R, Greene LW. Octreotide therapy for recurrent refractory hypoglycemia due to sulfonylurea

in diabetes-related kidney failure. Endocr Pract. 2007;13(4):417–23. https://doi.org/10.4158/EP.13.4.417.
43. Cabot J, Morrison J, Manini A. Prolonged, refractory glyburide and nateglinide toxicity in the setting of acute renal failure. In: XXXV International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT); 26–29 May 2015, St Julian's, Malta. Clin Toxicol. 2015;53(4):233–403. https://doi.org/10.3109/15563650.2015.1024953.
44. Kim T, Kim J, Leikin S, Leikin J. A case of prolonged hypoglycemia following glimepiride overdose using corresponding drug levels. Crit Care Med. 2019;47(1):p129. https://doi.org/10.1097/01.ccm.0000551049.51672.9c.
45. Carr R, Zed PJ. Octreotide for sulfonylurea-induced hypoglycemia following overdose. Ann Pharmacother. 2002;36(11):1727–32. https://doi.org/10.1345/aph.1C076.
46. Chinnappa P, Skugor M, Siraj E. Successful treatment of sulfonylurea-induced prolonged hypoglycemia with the use of octreotide. In: Abstracts for the American Association of Clinical Endocrinologists 12th Annual Meeting and Clinical Congress; May 14–18, 2003, San Diego, California, USA. Endocr Pract. 2003;9 Suppl 1:1–28. https://doi.org/10.4158/EP.9.S1.1.
47. Fleseriu M, Skugor M, Chinnappa P, Siraj ES. Successful treatment of sulfonylurea-induced prolonged hypoglycemia with the use of octreotide. Endocr Pract. 2006;12(6):635–40. https://doi.org/10.4158/EP.12.6.635.
48. Zaid AH, Sapru S, Costello J, Boradia C. Sulfonylurea induced severe hypoglycemia in a diabetic with renal failure— A case report. J Biosci Med. 2015;3(11):68–70. https://doi.org/10.4236/jbm.2015.311008.
49. Nakaya M, Oka R, Miyamoto S. Successful treatment of severe sulfonylurea-induced hypoglycemia by the subcutaneous administration of octreotide in an elderly patient with diabetes: a case report. Nihon Ronen Igakkai Zasshi. 2019;56(3):336–42.
50. Khan K, Qureshi S. Inadvertent sulfonylurea overdose and treatment with octreotide: a case report. Curr Tr Clin & Med Sci. 2019;1(2). https://doi.org/10.33552/CTCMS.2019.01.000509.
51. Braet C, Hussein Agha Y, Taleb A, Buess C, Millard J. Sulfonylurea-induced hypoglycemia in a patient with cirrhosis. Cureus. 2020;12(6):e8513. https://doi.org/10.7759/cureus.8513.
52. Nzerue CM, Thomas J, Volcy J, Edeki T. Use of octreotide to treat prolonged sulfonylurea-induced hypoglycemia in a patient with chronic renal failure. Int J Artif Organs. 2003;26(1):86–9. https://doi.org/10.1177/039139880302600113.
53. Igala S, Domingo A, Villafranca A, Gomez-Daspet J, Rivera L. Octreotide's role in managing intentional sulfonylurea overdose. In: Chavez C, Meléndez M, editors. Endocrine Society's 96th Annual Meeting and Expo; June 21–24, 2014, Chicago. Endocr Rev. 2013;35(supp 1):i1-i1153. https://doi.org/10.1093/edrv/35.supp.1.
54. Graudins A, Linden CH, Ferm RP. Diagnosis and treatment of sulfonylurea-induced hyperinsulinemic hypoglycemia. Am J Emerg Med. 1997;15(1):95–6. https://doi.org/10.1016/s0735-6757(97)90062-0.
55. Yamaguchi S, Ikejima M, Furukawa A, Abe M, Nakazaki M, Ishihara H. Octreotide for hypoglycemia caused by sulfonylurea and DPP-4 inhibitor. Diabetes Res Clin Pract. 2015;109(2):e8–10. https://doi.org/10.1016/j.diabres.2015.05.008.
56. Gunaratne K, Austin E, Wu PE. Unintentional sulfonylurea toxicity due to a drug-drug interaction: a case report. BMC Res Notes. 2018;11(1):331. https://doi.org/10.1186/s13104-018-3404-8.
57. Braatvedt GD. Octreotide for the treatment of sulfonylurea-induced hypoglycemia in type 2 diabetes. N Z Med J. 1997;110(1044):189–90.
58. Kothari A, Shah K. Role of octreotide in management of sulfonylurea-induced refractory hypoglycemia: a case report. Int J Sci Res. 2021;3–4. https://doi.org/10.36106/ijsr/9600245.
59. Khan M, Kathrada N, Nash D, Chowdhury D. A young man presenting with persistent hypoglycemia and reduced level of consciousness: case study with review of literature. World J Emerg Med. 2022;13(5):418–21. https://doi.org/10.5847/wjem.j.1920-8642.2022.074.
60. Ausman C, Grossart E, Shirazi FM, Smelski G. Reactive hypoglycemia during treatment of sulfonylurea overdose. In: North American Congress of Clinical Toxicology (NACCT) Abstracts 2021. Clin Toxicol. 2021;59(11):1037–1193. https://doi.org/10.1080/15563650.2021.1960683.
61. Sayed MA, Mustafa SB, Mushtaq J, Rehan M, Hussain S, Sadiq HM. Drug-induced hypoglycemia: a case of rare but life-threatening hypoglycemia with a combined use of glipizide and levofloxacin. In: Abstracts from the 2023 Annual Meeting of the Society of General Internal Medicine; 2023.
62. Barkin JA, Block HM, Mendez PE. Octreotide: a novel therapy for refractory sulfonylurea-induced hypoglycemia. Pancreas. 2013;42(4):722–3. https://doi.org/10.1097/MPA.0b013e3182769c26.
63. Abdullah T, Haedar A, Soenarto B. Octreotide treatment for hypoglycemic refractory case caused by sulfonylureas with impaired renal function. Jurnal Kedokteran Brawijaya. 2023;32(4):262–264. https://doi.org/10.21776/ub.jkb.2023.032.04.11.
64. Green RS, Palatnick W. Effectiveness of octreotide in a case of refractory sulfonylurea-induced hypoglycemia. J Emerg Med. 2003;25(3):283–7. https://doi.org/10.1016/s0736-4679(03)00204-x.
65. Crawford BAL, Perera C. Octreotide treatment for sulfonylurea-induced hypoglycaemia. Med J Aust. 2004;180(10):540–1. https://doi.org/10.5694/j.1326-5377.2004.tb06064.x.
66. Covvey JR, Lewis DA. Glimepiride-induced hypoglycemia with ciprofloxacin, metronidazole, and acute kidney injury. Hosp Pharm. 2010;45(12):934–8. https://doi.org/10.1310/hpj4512-934.
67. Bui L, Adler D, Keller K. Prolonged octreotide infusion to treat glyburide-induced hypoglycemia. In: 2000 North American Congress of Clinical Toxicology Annual Meeting. J Toxicol Clin Toxicol. 2000;38(5):485–594. https://doi.org/10.1081/clt-1001020075.
68. Yanta J, Menke N, King A, Pizon A. Refractory hypoglycemia in an acetaminophen, acetyl-salicylic acid, and glyburide overdose. In: 2012 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT); Oct 1–6, 2012; Las Vegas, NV, USA. Clin Toxicol. 2012;50(7):574–720. https://doi.org/10.3109/15563650.2012.700015.
69. Pelavin PI, Abramson E, Pon S, Vogiatzi MG. Extended-release glipizide overdose presenting with delayed hypoglycemia and treated with subcutaneous octreotide. J Pediatr Endocrinol Metab. 2009;22(2):171–5. https://doi.org/10.1515/jpem.2009.22.2.171.
70. Lugassy D, Nelson L, Hoffman R, Howland M. Failure of standard octreotide dosing to prevent recurrent hypoglycemia following sulfonylurea exposure in a child. In: Abstracts. Clin Toxicol. 2009;47(7):702–765. https://doi.org/10.1080/15563650903076924.
71. Glatstein M, Garcia-Bournissen F, Scolnik D, Koren G. Sulfonylurea intoxication at a tertiary care pediatric hospital. Can J Clin Pharmacol. 2010;17(1):e51-56.
72. Muller AA. Small amounts of some drugs can be toxic to young children: one pill or one swallow can require aggressive treatment. J Emerg Nurs. 2003;29(3):290–3. https://doi.org/10.1067/men.2003.82.
73 Blume-Odom C, Scalzo A, Weber J. Euglycemia after late octreotide use in pediatric glipizide toxicity. In: Abstracts. Clin Toxicol. 2010;48(6):604–67. https://doi.org/10.3109/15563650.2010.493290.
74. Kumar S, Choudhary A, Ali M, Gupta V, Muralidharan J, Singhi S. Sulfonylurea poisoning in a healthy toddler. Indian J Pediatr. 2017;84(2):147–9. https://doi.org/10.1007/s12098-016-2249-1.

75. Mordel A, Sivilotti M, Old A, Ferm R. Octreotide for pediatric sulfonylurea poisoning. In: 1998 North American Congress of Clinical Toxicology Annual Meeting; Sep 9–15, 1998; Orlando, Florida, USA. Abstracts. J Toxicol Clin Toxicol. 1998;36(5):427–537.
76. Calello DP, Kelly A, Osterhoudt KC. Case files of the Medical Toxicology Fellowship Training Program at the Children's Hospital of Philadelphia: a pediatric exploratory sulfonylurea ingestion. J Med Toxicol. 2006;2(1):19–24. https://doi.org/10.1007/BF03161009.
77. Kent D, Main B, Friesen M. Use of octreotide in sulfonylurea poisoning in a child. In: Abstracts of the North American Congress of Clinical Toxicology Annual Meeting; Sep 4–9, 2003; Chicago, Illinois, USA. J Toxicol Clin Toxicol. 2003;41(5):641–770. https://doi.org/10.1081/clt-120024368.
78. Rath S, Bar-Zeev N, Anderson K, Fahy R, Roseby R. Octreotide in children with hypoglycemia due to sulfonylurea ingestion. J Paediatr Child Health. 2008;44(6):383–4. https://doi.org/10.1111/j.1440-1754.2008.01339.x.
79. Escajeda J, King A, Menke N, Katz K, Pizon A. Continuous octreotide infusion effectively prevents hypoglycemia in resistant pediatric sulfonylurea toxicity. In: Chavez C, Meléndez M, editors. Abstracts of the 2013 ACMT Annual Scientific Meeting; Mar 15–17, 2013; San Juan, Puerto Rico, US. J Med Toxicol. 2013;9(1):82–105. https://doi.org/10.1007/s13181-012-0282-7.