Indian Journal of Clinical Practice, Vol. 31, No. 10, March 2021

Posology of Antidiabetic Drugs and Insulins: A Review of Standard Textbooks

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ABSTRACT

Objectives: The aim of this bibliographic review is to assess whether standard pharmacology, endocrinology and diabetology textbooks adequately mention the details regarding timings of administration, frequency and dose of various oral and injectable antidiabetic drugs. **Material and methods:** Four standard textbooks of pharmacology, two of diabetology and three of endocrinology were assessed for the published information regarding dose, timing and frequency of antidiabetic drugs. **Results:** Various omissions and contraindications were found in the coverage of glucose-lowering drugs in standard textbooks. Proper timing and frequency of administration of sulfonylureas, thiazolidinediones, SGLT2 inhibitors, GLP receptor agonists and DPP-4 inhibitors have been omitted in majority of the textbooks. **Conclusions:** This article stresses upon the need of a uniform source of information for providing adequate and standardized knowledge regarding timing, frequency and dose of antidiabetic drugs.

Keywords: Posology, antidiabetic drugs, postprandial hyperglycemia

Correct timing of glucose-lowering therapy is an important aspect of diabetes pharmacotherapeutics. Matching the dose of a particular drug with meals depends upon its mechanism of action and pharmacokinetic profile. This timing varies from class-to-class and drug-to-drug. Each drug has a specific time action profile. This should match with food absorption. Inappropriate timing/frequency/dose of administration may lead to unwanted hyperglycemia or hypoglycemia leading onto poor glycemic control or complications in the patients.

This glycemic variability is easily avoidable with the better knowledge and understanding of appropriate dose, timing of administration and frequency of drug administration. Pharmacology, diabetology and endocrinology textbooks are an important and reliable source of such information, both for students and clinicians. This article aims at assessing the adequacy of the knowledge provided by these textbooks regarding posology (i.e., dose, frequency and timing of antidiabetic drugs).

MATERIAL AND METHODS

Some of the most popular and most commonly read textbooks of pharmacology, diabetology and endocrinology were included in the study. Four standard textbooks of pharmacology (2 by Indian authors and 2 by US authors) were analyzed. Two textbooks of diabetology were also studied, out of which 1 textbook is by Indian author and other is by US author. Three textbooks of endocrinology (2 US and 1 Indian in origin) were also assessed for the desired information. Latest available editions of the textbooks were taken for analysis.

RESULTS

The results of the analysis have been tabulated in Table 1, which shows the comparison of information about antidiabetic drugs available in different textbooks.

DISCUSSION

This bibliometric analysis highlights various omissions and contraindications in the coverage of glucose-lowering drugs in standard textbooks.

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Table 1. Comparison of Information in Pharmacology, Endocrinology and Diabetology Textbooks

Drug class	Drug	Goodman and Gilman's the Pharmaceutical Basis of Therapeutics[1]	Basic and Clinical Pharmacology[2]	Essentials of Medical Pharmacology[3]	Principles of Pharmacology[4]	Endocrino-logy[5]	Textbook of Diabetes[6,7]	RSSDI Text book of Diabetes Mellitus[8-10]	Manual of Clinical Endocrino-logy[11]	Williams Textbook of Endocrino-logy[12]
Biguanides	Metformin	0.5-2.5 g b.i.d., with meals	500 mg-2.55 g at bedtime for fasting hyperglycemia and before meals for postprandial hyperglycemia	0.5-2.5 mg, 1-2 doses per day	500 mg before breakfast and 500 mg with evening meal	Start with 500 mg o.d. Titrate up to 500-1,000 g b.i.d., given with meals	500 mg o.d.-2,550 mg (divided doses) with meals or immediately before meals[6]	-	500 mg o.d. to 2,500 mg in divided doses	At least b.i.d.
	Metformin SR	Max dose is 2 g o.d., with meals	-	-`	-	With evening meal	Once-daily in morning or b.i.d. (morning and evening)[6]	-	-	-
Thiazolidine-diones	Pioglitazone	15-45 mg o.d.	15-45 mg o.d.	15-45 mg o.d.	11-45 mg o.d.	15-45 mg daily	15-45 mg/day[6]	-	15-45 mg/ day o.d.	-
	Rosiglitazone	4-8 mg o.d.	2-8 mg o.d. or b.i.d.	-	4-8 mg o.d.	2-8 mg daily	4-8 mg[6]	-	-	-
Meglitinide analog	Repaglinide	0.5-16 mg preprandially	0.25-4 mg, just before each meal (max 16 mg/day)	1-8 mg, 3-4 doses/day, before each major meal	0.25-4 mg shortly before each meal	0.5-2 mg t.i.d. with each meal	0.5-4 mg, 15-30 min before each main meal[6]	0.5-4 mg in 3-4 doses, just before or soon after starting a meal[8]	Preprandial dosing	Max 4 mg with each meal
	Nateglinide	180-360 mg, 1-10 min before a meal	60-120 mg, just before meals	180-480 mg, 3-4 doses per day, 10 min before meal	60-120 mg, shortly before each meal	60-120 mg t.i.d. with each meal	60-180 mg t.d.s., preprandial use[6]	60-180 mg in 3-4 doses, just before or soon after starting a meal[8]	Preprandial dosing	120 mg with each meal
Sulfonylureas	Glipizide	5-40 mg o.d. or b.i.d.	5-30 mg, 30 min before breakfast	5-20 mg, o.d. or b.i.d.	5-20 mg o.d. or b.i.d.	2.5-5 mg initially. Max 40 mg divided b.i.d.	2.5-20 mg[6]	1.25-15 mg in 2-3 doses, 20-30 min before meals[8]	5-40 mg/day	Initial 5 mg, Max 40 mg, divided b.i.d.
	Glipizide extended release	5-20 mg daily	Once-daily morning dose, max 20 mg/day	-	-	2.5-5 mg initially. 20 mg o.d. max dose	Once-daily dose[6]	-	5-20 mg/day	Initial 5 mg. Max 20 mg o.d.
	Gliclazide	-	-	40-240 mg, o.d. or b.i.d.	40-250 mg o.d. or b.i.d.	-	40-320 mg[6]	40-240 mg in 1-3 doses, 20-30 min before meals[8]	-	-

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	Gliclazide MR	-	-	-	-	-	30-120 mg o.d.[6]	-	-	-
	Glyburide (glibenclamide)	1.25-20 mg o.d. or b.i.d.	1.25-20 mg, single morning dose	2.5-15 mg o.d. or b.i.d.	5-15 mg o.d. or b.i.d.	1.25-5 mg initially. Max dose 20 mg, divided b.i.d.	1.25- 15 mg[6]	1.25-20 mg in 1-3 doses/day, 20-30 min before meals[8]	1.25-20 mg/day	Initial dose 2.5 mg. Max dose 20 mg, divided b.i.d.
	Micronized glyburide	0.75-12 mg daily	-	-	-	1.5-3 mg initial dose. Max dose is 6 mg, b.i.d.	-	-	0.75-12 mg/day	Initial 3 mg. Max 6 mg b.i.d.
	Glimepiride	1-8 mg o.d.	1-8 mg o.d.	1-6 mg o.d. or b.i.d.	1-6 mg o.d.	1-2 mg initially. Maximum dose is 8 mg o.d.	1-6 mg[6]	1-8 mg o.d., 20-30 min before meals[8]	1-8 mg/day	1-8 mg o.d.
α-Glucosidase inhibitors	Acarbose	25-100 mg, before meals	25-100 mg, just before ingesting the final portion of each meal	50-100 mg t.d.s., at the beginning of each major meal	50-100 mg t.d.s. at the beginning of each major meal	25-100 mg t.i.d. with first bite of carbohydrate containing meal	50 mg o.d. to 200 mg t.d.s., with meals[6]	25 mg t.d.s. at the start of each main meal to max of 100 mg t.d.s.[9]	-	-
	Voglibose	-	-	200-300 mg t.d.s. just before meals	-	-	With meals[6]	0.2 mg t.d.s., just before each meal - max of 0.3 mg t.d.s.[9]	-	-
	Miglitol	25-100 mg before meals	25-100 mg just before ingesting the final portion of each meal	25-100 mg t.d.s. at the beginning of each major meal	-	25-100 mg t.i.d. with first bite of carbohydrate containing meal	With meals[6]	-	-	-
DPP-4 inhibitors	Vildagliptin	50-100 mg daily	-	50-100 mg o.d. or b.i.d.	50 mg o.d. before meals	-	50 mg b.i.d.[6]	50 mg o.d. or b.i.d., with or without food[10]	50 mg b.i.d.	-
	Linagliptin	-	-	-	-	-	-	-	5 mg/day	-
	Sitagliptin	100 mg daily	100 mg orally o.d.	100 mg o.d.	100 mg o.d. before meals	25-100 mg o.d.	100 mg o.d. in morning[6]	100 mg o.d.[10]	100 mg/day	-
	Saxagliptin	2.5-5 mg daily	2.5-5 mg daily	5 mg o.d.	-	25-100 mg daily	-	5 mg/day[10]	-	-
	Alogliptin	-	-	-	-	-	-	12.5-25 mg[10]	12.5-25 mg/day	-

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GLP receptor agonist	Exenatide	0.01-0.02 mg s/c inj, before meals	5-10 µg s/c b.i.d. inj, within 60 min before a meal	s/c inj	5-10 µg b.i.d., 30-60 min before meals	5-10 µg b.i.d. s/c up to 60 min before main meals	5-10 µg b.i.d. within 60 min of morning and evening meals[7]	-	5-10 µg b.i.d., s/c, 60 min prior to meals	-
	Exenatide QW	-	-	-	-	-	Once weekly[7]	Once weekly[10]	Once weekly	-
	Liraglutide	s/c inj o.d.	Started at 0.6 mg injectable dose	s/c inj once-daily	-	-	-	Once-daily[10]	0.6-1.8 mg/day	-
	Albiglutide	-	-	-	-	-	30 mg weekly[7]	-	-	-
	Dulaglutide	-	-	-	-	-	-	Once weekly[10]	-	-
	Semaglutide	-	-	-	-	-	-	-	Once weekly	-
	Lixisenatide	-	-	-	-	-	-	-	-	-
SGLT2 inhibitor	Dapaglifozin	-	-	o.d.	-	-	-	-	-	-
	Canagliflozin	-	-	-	-	-	-	-	-	-
	Ipragliflozin	-	-	-	-	-	-	-	-	-
Dopamine D2 receptor agonist	Bromocriptine	1.6-4.8 mg, with food in the morning within 2 h of awakening	-	0.8-4.8 mg o.d., early in the morning	-	-	-	1.6-4.8 mg o.d. within 2 h after waking in the morning, with food[9]	-	Within 2 h of rising in the morning
Amylin analog	Pramlintide	15-60 µg s/c inj in type 1 DM, 60-120 µg s/c inj in type 2 DM. Injected prior to meals	15-60 µg s/c inj in type 1 DM, 60-120 µg s/c inj in type 2 DM. Injected immediately before eating	s/c inj before meal	15-60 µg s/c inj before meals as an adjunct to insulin in DM type 1 cases and 60-120 µg s/c inj before meals with insulin in type 2 DM.	60-120 µg t.i.d. (for DM type 2), 15-30 µg (for DM type 1), s/c before meals	60-90 µg, 3-4 times/day s/c prior to meals (type 1 DM). Higher doses s/c b.i.d. in type 2 DM[7]	-	-	15-60 µg before meals in type 1 DM; max 120 µg before meals in type 2 DM
Bile acid binding resin	Colesevelam	3 tab (625 mg) b.i.d. before lunch and dinner or 6 tab prior to largest meal	1,875 mg b.i.d. or 3,750 mg o.d. orally	-	-	-	-	-	-	-

Metformin is covered well by 8 out of 9 textbooks, with 6 of them mentioning relatively concordant doses, and 2 describing only frequency of administration. Timing of administration was reported by 5 books. Metformin SR preparation was listed by only 3 textbooks, both American in origin, though its use is widespread across the world. Pioglitazone usage is covered in 7 textbooks, with similar dosages, but relationship with meal timings is not stated by any author.[6]

Rosiglitazone, which is used in a restricted subset of patients, is covered by 5 texts. But none of the textbooks mention timings of this drug. The omission of this molecule's details from majority of endocrinology and diabetology books reflects the decline in its popularity. Meglitinide analogs are discussed in uniform detail by all 9 textbooks surveyed. This is a pleasant (and perhaps superfluous) exercise, as nateglinide is rarely used in clinical practice and repaglinide is relatively less commonly prescribed than sulfonylureas.

Sulfonylureas are the oldest class of glucose-lowering drugs currently in use. A large number of drugs and preparations are available, and are well-covered by most textbooks. Micronized glyburide, glipizide ER and gliclazide, which are not available in all countries, are discussed by relatively less authors (5 and 4, respectively). While information related to glipizide and glibenclamide is uniform in most books, there is conflicting advice regarding the frequency of dosage of glimepiride. Timing of administration is not mentioned by many authors. A blanket recommendation to prescribe all sulfonylureas 20-30 minutes before meals is given by the leading Indian textbook of diabetes. The maximum dose of glimepiride is mentioned as 6 mg by three, and 8 mg by six authors. This may reflect the difference in maximum doses approved by various regulatory authorities. A similar lack of consensus is seen for gliclazide, where maximum doses vary from 240 to 320 mg and frequency of dosage ranges from 1 to 3 per day.

Alpha-glucosidase inhibitors are discussed in detail by seven (acarbose), four (miglitol) and two (voglibose) authors. Most of the advice contained in these texts is concordant with each other. The dipeptidyl peptidase-4 (DPP-4) inhibitors are relatively newer class of drugs, which may explain why their dose is not mentioned in many texts. The timing of administration; however, is written differently in various books. While some authors omit this aspect of posology, others recommend vildagliptin and sitagliptin before meals, and yet others advise no regard to meal times. The glucagon-like peptide-1 (GLP-1) receptor agonists are covered by some, but not all, books. While exenatide's timing of administration is discussed by six authors, no book makes mention of the timing of dosage of liraglutide. New once-weekly GLP-1 receptor agonists are discussed by one (dulaglutide, semaglutide) and three (exenatide QW) textbooks. Bromocriptine and colesevelam are nondiabetic drugs, which have recently been approved for use in type 2 diabetes. They are prescribed infrequently. While four books mention bromocriptine, in a uniform manner, only two US textbook covers colesevelam. This poor coverage reflects the poor availability of this molecule. Another molecule which has limited availability, relevance and usage, is pramlintide. Approved for the management of postprandial hyperglycemia in both type 1 and type 2 diabetes, this is well-described, in a similar manner, by five texts. Sodium glucose co-transporter 2 (SGLT2) inhibitors, which are the latest class of oral glucose-lowering drugs, have found mention in one current US pharmacology textbook.

CONCLUSION

This bibliometric analysis highlights the need to have standardized, uniform sources of information regarding posology of glucose-lowering drugs. Such information will be of importance to students and professionals of diabetology, and will benefit their patients as well.

LIMITATIONS

All textbooks of pharmacology, diabetology and endocrinology were not analyzed for the review. However, the textbooks analyzed here are the most commonly used ones.

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Some Type 2 Diabetes Patients have Major ECG Abnormalities

Investigators noted major ECG abnormalities in 13% of over 8,000 unselected patients with type 2 diabetes in a community-based Dutch cohort. There was a 9% prevalence of major abnormality in the subgroup of these patients without identified cardiovascular disease (CVD). It was noted that minor ECG abnormalities were even more common.

The study obtained data from 8,068 patients with type 2 diabetes, enrolled in the prospective Hoorn Diabetes Care System cohort. Major abnormality was noted in 13%, while 16% had a minor abnormality. The most common types of abnormalities included ventricular conduction defects (14%) and arrhythmias (11%). In the subgroup of patients with no history of CVD, 9% were found to have a major abnormality while 15% had a minor abnormality. The findings are published in the *Journal of Diabetes and Its Complications*… (*Medscape*)

COVID-19 Vaccines Reach Sudan and Rwanda Through COVAX

Through the COVAX vaccine facility, Sudan and Rwanda have become the latest countries to receive the COVID-19 vaccines, stated UN agencies.

Overall, 8,00,000 doses of the AstraZeneca vaccine arrived in Khartoum as Sudan became the first country in the Middle East and North Africa region to receive the vaccine through COVAX. Rwanda received 2,40,000 doses of the AstraZeneca vaccine and expects to receive 1,02,000 more doses from Pfizer-BioNTech. Both the countries will start the vaccine drive initially targeting essential health workers and vulnerable people.

Julianna Lindsey Children, UNICEF Representative in Rwanda, called it an historic moment, and stated that people across the country can now breathe a sigh of relief knowing that the nation is moving towards recovering from the COVID-19 pandemic… (*UN*)

Bharat Biotech Says Its COVID-19 Vaccine Shows 81% Efficacy

Bharat Biotech's COVID-19 vaccine has shown an interim efficacy of 81% in late-stage clinical trials, reported the company.

The interim analysis included 43 recorded cases of COVID-19 in a trial of 25,800 participants. Thirty-six of these 43 cases were noted in participants in the placebo group, while 7 cases were recorded in those who received the Bharat Biotech vaccine. This translated to an efficacy rate of 80.6%.

India had approved the Bharat Biotech vaccine, called COVAXIN, in January without late-stage efficacy data. The vaccination drive in the country includes COVAXIN as well as a vaccine developed by Oxford University and AstraZeneca. Earlier this week, Prime Minister Narendra Modi was also given the first dose of COVAXIN… (*ET Healthworld – Reuters*)