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Dapagliflozin

Prop INN; USAN

SGLT2 Inhibitor
Antidiabetic Agent

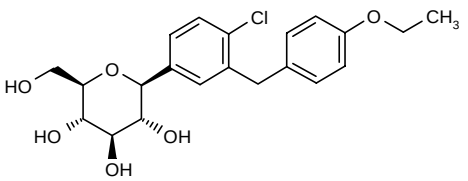
BMS-512148

1-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-1-deoxy-β-D-glucopyranose

(1*S*)-1,5-Anhydro-1-*C*-[4-chloro-3-(4-ethoxybenzyl)phenyl]-D-glucitol

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol

InChI=1/C21H25ClO6/c1-2-27-15-6-3-12(4-7-15)9-14-10-13(5-8-16(14)22)21-20(26)19(25)18(24)17(11-23)28-21/h3-8,10,17-21,23-26H,2,9,11H2,1H3/t17-,18-,19+,20-,21+/m1/s1



$C_{21}H_{25}ClO_6$
Mol wt: 408.873

CAS: 461432-26-8

EN: 356099

Abstract

Diabetes is a growing epidemic for which new treatments are needed as it is often not controlled with current therapies. One potential means of treating diabetes is via modulation of glucose uptake. A novel strategy for achieving this is through inhibition of sodium-dependent glucose transporters (SGLTs), which mediate the process by which plasma glucose filtered in the kidney glomerulus is reabsorbed. The great majority of this process of reabsorption is mediated by SGLT2 and SGLT2 inhibitors have therefore been sought and identified in order to prevent renal glucose reabsorption and increase glucose excretion in urine. The compound that has advanced the furthest is dapagliflozin, which demonstrated superior metabolic stability compared to early agents. Dapagliflozin also exhibited potent inhibition of SGLT2 and selectivity over SGLT1 *in vitro*, and was associated with reduced plasma glucose levels in animal models of diabetes after acute and chronic dosing. Dapagliflozin has proven safe and well tolerated in humans, with pharmacokinetic and pharmacodynamic variables indicating that daily dosing is appropriate. Double-blind trials in patients with type 2 diabetes revealed reductions in fasting and postprandial glucose, as well as significant reductions in HbA1c. Dapagliflozin has entered phase III evaluation.

Synthesis

Dapagliflozin can be synthesized as follows: 2-Chloro-5-bromobenzoic acid (I) is chlorinated with oxalyl chloride and catalytic DMF in CH_2Cl_2 to afford the benzoyl chloride derivative (II), which is subjected to Friedel-Crafts reaction with ethoxybenzene (III) in the presence of $AlCl_3$ in CH_2Cl_2 to give the benzophenone derivative (IV). Subsequent decarbonylation of ketone (IV) employing triethylsilane and boron trifluoride etherate in acetonitrile yields 5-bromo-2-chloro-4'-ethoxydiphenylmethane (V). The lithiated derivative of bisarylmethane (V) (generated by treatment with BuLi in THF/toluene at –78 ºC) is coupled with the persilylated lactone (VII) (obtained from D-gluconolactone [VI] by treatment with trimethylsilyl chloride and NMM in THF) to yield the corresponding lactol adduct, which is deprotected *in situ* with methanesulfonic acid in MeOH to afford the desilylated ketal (VIII) (1-3). Polyol (VIII) is peracetylated with acetic anhydride and DIEA in THF resulting in the tetraacetate (IX). The glucosidic methoxy group of (IX) is then reductively removed using triethylsilane and boron trifluoride etherate in water/acetonitrile to give the glucoside (X) (1, 2), which is finally deacetylated by treatment with LiOH in aqueous MeOH (1-3).

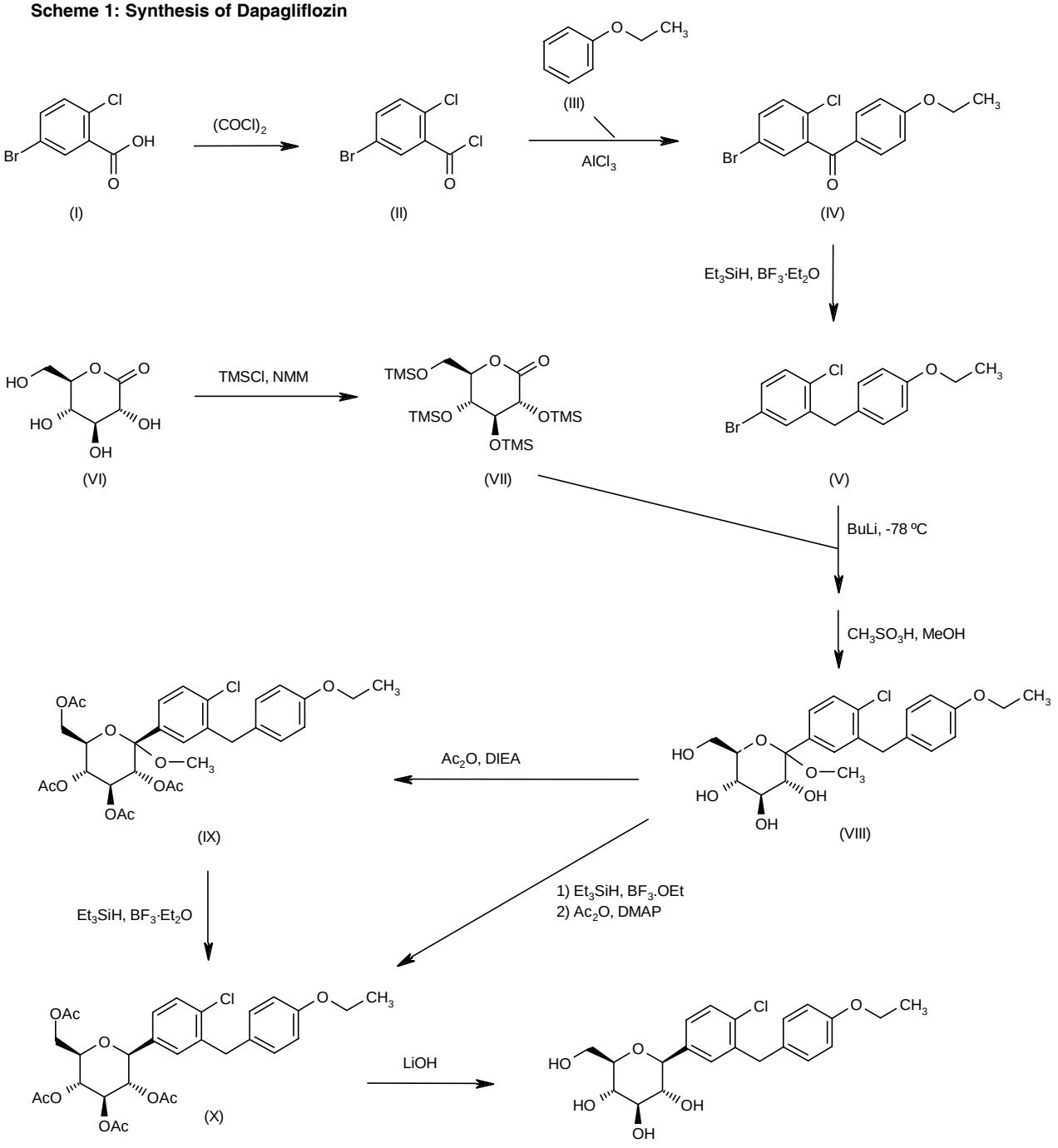
Alternatively, intermediate (X) can be prepared by reduction of the glucosidic methoxy group of (VIII) with trethylsilane and boron trifluoride etherate in CH_2Cl_2/acetonitrite, and subsequent peracetylation with Ac_2O, DMAP in CH_2Cl_2/pyridine (3).

Background

The widespread prevalence of diabetes and its increasing incidence may mean that we run the risk of the disease becoming an accepted fact of life. It is estimated that 23.6 million people in the United States have dia-

P. Cole, M. Vicente, R. Castañer. Prous Science, Provenza 388, 08025 Barcelona, Spain.

Scheme 1: Synthesis of Dapagliflozin



betes, or 7.8% of the total population (4), and a 2005 estimate of the prevalence of diabetes worldwide put the figure at 217 million (5). Costs in 2007 in the U.S. alone were estimated to be USD 174 billion (6). Most of the major pharmaceutical companies are involved in research related to diabetes treatment. Part of the attraction may be that diabetes represents a growth market: it has been estimated that by the year 2050 there will be 48.3 million people with diagnosed diabetes in the United States, an increase of 51% (7). The worldwide prevalence of diabetes is expected to grow to 366 million by 2030, representing an increase of roughly 40% in 25 years (5, 8). In the developing world, the prevalence of diabetes is predicted to increase by 170% between 1995 and 2025, while the increase in the developed world is expected to be 42% during this period (9).

The hyperglycemia resulting from diabetes has severe consequences for both society and the individual. Atherosclerosis, heart disease, stroke, hypertension, end-stage renal disease, retinopathy leading to blindness, nervous system damage, sexual dysfunction, periodontal disease, frequent infections and difficult-to-treat foot ulcers are common complications and comorbidities associated with the disease. Not surprisingly, the risk of death increases and life expectancy decreases in patients with diabetes. One population-control study found life expectancy to be reduced 12.8 and 12.2 years, respectively, in men and women with diabetes compared to men and women without diabetes (10).

The progressive nature of the disease and the limited efficacy of treatments were both highlighted in the United Kingdom Prospective Diabetes Study (UKPDS), where it was reported that typically only 25-50% of type 2 diabetes patients are effectively treated with current therapies. On a positive note, the UKPDS also showed that aggressive treatment of the disease can reduce morbidity and mortality, with microvascular complications reduced 25% with intensive therapy (11-13).

One novel approach to treating diabetes involves inhibition of sodium-dependent glucose transporters (SGLTs). Over 99% of plasma glucose filtered in the kidney glomerulus is reabsorbed, and this process is mediated by SGLT1 and SGLT2, mainly the latter. Inhibition of SGLT2 may therefore normalize plasma glucose levels in diabetes patients by preventing renal reabsorption and increasing urinary excretion of glucose. SGLT2, but not SGLT1, mutations have been found to be associated with renal glucosuria. It has been predicted that inhibition of SGLT1, but not SGLT2, would be associated with gastrointestinal adverse effects. SGLT2 inhibition is thought to carry a low risk of hypoglycemia as it does not interfere with the normal counterregulatory mechanisms for glucose (14-19).

In early research, a number of compounds inhibiting SGLT2 were identified which improved hyperglycemia in animal models, but these were limited by metabolic instability. Investigation of the cause of this characteristic and the resulting structural alterations led to the development of metabolically stable SGLT2 inhibitors and the discovery of dapagliflozin (BMS-512148) (3, 20-22).

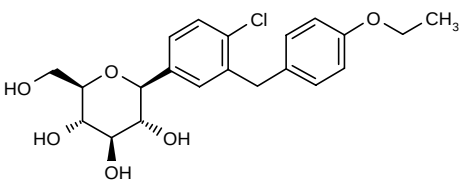
The promise of inhibition of SGLT2 as a means of treating type 2 diabetes is revealed by the number of agents with this mechanism of action that are under development (Table I). This mechanism has received widespread attention in the pharmaceutical industry, with several of the industry's largest players taking part in the development of these agents. Of these agents, only dapagliflozin has reached phase III at present.

Preclinical Pharmacology

In *in vitro* studies conducted to evaluate the inhibitory potential of dapagliflozin, inhibition of the accumulation of radiolabeled α-methyl-D-glucopyranoside in Chinese hamster ovary (CHO) cells stably expressing human or rat SGLT1 and SGLT2 was assessed. The EC_{50} values for dapagliflozin were 1.1 nM for human SGLT2 and 1.4 μM for human SGLT1, with approximately 1,200-fold selectivity for SGLT2 relative to SGLT1. Dapagliflozin demonstrated similar potency against rat and human

Table I: SGLT2 inhibitors currently under development for the treatment of diabetes (from Prous Science Integrity®).

Drug	Source	Phase
1. Dapagliflozin	Bristol-Myers Squibb/AstraZeneca	III
2. ASP-1941*	Astellas Pharma/Kotobuki	II
3. AVE-2268*	sanofi-aventis	II
4. JNJ-28431754*	Johnson & Johnson	II
5. Remogliflozin etabonate	GlaxoSmithKline/Kissei	II
6. TA-7284*	Mitsubishi Tanabe Pharma/Johnson & Johnson	II
7. YM-543*	Astellas Pharma/Kotobuki	II
8. R-7201*	Roche/Chugai Pharmaceutical	I
9. SAR-7226*	sanofi-aventis	I
10. ISIS-388626*	Isis Pharmaceuticals	Preclinical



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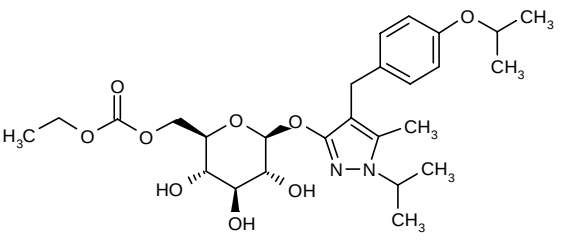

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*Structure not yet available.

SGLT2, although the selectivity for rat SGLT2 *versus* rat SGLT1 decreased greatly (approximately 200-fold). Dapagliflozin demonstrated greater potency in inhibiting human SGLT2 and greater selectivity for SGLT2 over SGLT1 than other SGLT inhibitors, such as the natural product phlorizin, a nonselective inhibitor. At 20 μM, dapagliflozin only weakly (8%) inhibited 2-deoxyglucose uptake in human adipocytes mediated by glucose transporters GLUT-1 or GLUT-4 (3, 22).

When normal rats received oral dapagliflozin doses of 0.01-10 mg/kg, significant and dose-dependent glucosuria was observed over a 24-h period, with a 1,000- to 10,000-fold increase in glucose disposal compared to vehicle-treated controls. Single oral doses of 0.1, 1.0 and 10 mg/kg induced losses of 550, 1100 and 1900 mg, respectively, of glucose per 200 g of body weight over 24 h. The difference in glucosuric potency of dapagliflozin compared to other initially developed SGLT inhibitors (*O*-arylglucosides) was greater than the difference in *in vitro* potencies, perhaps due to the greater metabolic stability of dapagliflozin resulting from replacement of the oxygen linkage between the glucose and aglycone moieties with a carbon linkage. In Zucker diabetic fatty rats, a dose-dependent increase in urine glucose and urine volume excretion was seen 6 h after administration of single oral doses of dapagliflozin of 0.01-1.0 mg/kg, which was also associated with reductions in plasma glucose. At 24 h, urinary glucose levels were doubled with all dapagliflozin doses compared with vehicle treatment. With a dapagliflozin dose of 1 mg/kg, reduced plasma glucose was seen 24 h postdose even after a period of refeeding. There were no signs of hypoglycemia in these experiments (3, 21, 22).

In rats with streptozotocin-induced diabetes, a single oral dose of 0.1 mg/kg of dapagliflozin was associated with a 55% reduction in blood glucose levels compared to vehicle controls after 5 h. Single doses of 0.01 and 0.03 mg/kg were associated with 17% and 45% reductions, respectively, at 5 h postdose in the same model (3, 21).

Chronic, once-daily dosing with 0.01-1.0 mg/kg was studied in Zucker diabetic fatty rats and dose-dependent decreases in fasting glucose levels were seen by day 8 of treatment when measured 24 h after the previous dose. Reduced glucose levels were also seen on day 15 of treatment after fasting for 24 h, and in fed animals assessed on day 14. These animals did not display changes in body weight or abnormal behavior compared with controls. After 15 days of treatment with dapagliflozin 0.5 mg/kg, Zucker diabetic fatty rats also had a 53% decrease in 18-h fasting plasma glucose levels when assessed 24 h after the final dose. In a hyperinsulinemic euglycemic clamp study conducted on the third day after the final dose, the rats displayed improved glucose utilization, reduced glucose production and enhanced glucose influx into liver tissue. Dapagliflozin treatment may therefore have beneficial metabolic effects beyond improving hyperglycemia. Glucose uptake into skeletal muscle and white adipose tissue was not significantly affected by the treatment (22).

Pharmacokinetics and Metabolism

The absorption, distribution, metabolism and excretion of dapagliflozin have also been studied. In rat and human serum, at 10 μM the free fraction of dapagliflozin was 3% and 4%, respectively. Oral bioavailability in humans was suggested by a high (> 150 nm/s) permeability value in Caco-2 cell monolayers and 84% oral bioavailability in rats. Steady-state volume of distribution was greater than the total blood volume in rats, and low to intermediate *in vitro* metabolic rates were seen after incubation of dapagliflozin with liver microsomes and hepatocytes from rats and humans. Oral administration of dapagliflozin 1 mg/kg to rats yielded a C_{max} of 0.6 μg/ml at 1.7 h and a systemic clearance rate of 4.8 ml/min/kg. Intravenous administration to rats, dogs and monkeys was associated with elimination half-lives of 4.6, 7.4 and 3.0 h, respectively (3, 21).

The pharmacokinetics of dapagliflozin have been assessed in healthy volunteers in single- and multiple-dose studies. In the single-dose study, oral doses of 2.5, 5, 10, 20, 50, 100, 250 and 500 mg or placebo were administered to 64 subjects after an overnight fast. Dose escalation was allowed when each dose was found to be safe and well tolerated. C_{max} increased slightly less and the AUC_{inf} increased slightly greater than dose-proportionally. Subjects in the 250-mg dose group were retreated with dapagliflozin 250 mg or placebo after a 7-day washout period and approximately 5 min after a high-fat breakfast. Compared to the fasted state, the median t_{max} was delayed 2.5 h, the geometric mean C_{max} was 39% lower and the AUC_{inf} was 7% lower with administration of 250 mg dapagliflozin after a high-fat meal (23).

Forty healthy volunteers were included in the multiple-dose study, where once-daily oral doses of 2.5, 10, 20, 50 and 100 mg or placebo were given for 14 days. A diet with a fixed amount of calcium and sodium chloride was also provided. Dapagliflozin exposure was proportional with dose, and an accumulation index of approximately 1.25 was noted with repeated dosing (24).

Data from two randomized, double-blind, placebo-controlled studies found the pharmacokinetics of dapagliflozin to be similar in healthy subjects and patients with type 2 diabetes. The studies evaluated dapagliflozin doses of 2.5-100 mg given once daily for 2 weeks in 30 healthy subjects and 38 diabetic patients. A 2-compartment model with first-order absorption and proportional residual error adequately described dapagliflozin pharmacokinetics. Clearance estimates were 20.2 and 19.1 l/h, respectively, for healthy subjects and diabetic patients. Covariates, including age, gender, body weight, disease status and creatinine clearance, did not have more than a 20% effect on dapagliflozin pharmacokinetic parameters (25).

Safety

Data from the dose-escalation study in 64 healthy volunteers cited above indicated that single doses of 2.5-

500 mg were safe and well tolerated. There were 22 adverse events in 14 subjects, with rates of 21% and 25%, respectively, among those given dapagliflozin and placebo. Adverse events were mostly mild to moderate in severity. Laboratory abnormalities were noted in 38 subjects; there were 31 cases of elevated urinary glucose, an expected effect given the mechanism of action of dapagliflozin (23).

Dapagliflozin doses of 2.5, 10, 20, 50 and 100 mg were also safe and well tolerated when given once daily for 14 days in the pharmacokinetic, pharmacodynamic and safety study also mentioned above. There were 24 adverse events in 16 subjects, with rates of 36.7% in the dapagliflozin group and 50% in the placebo group. All were mild to moderate, and the most frequently reported was rash. Dapagliflozin did not appear to affect renal safety markers, the Q-T_c interval or urinary excretion of magnesium, amino acids, calcium, chloride, oxalate, potassium, phosphate, sodium, uric acid, NAG (*N*-acetyl-β-D-glucosaminidase) or β_2-microglobulin (24).

In a randomized, double-blind, placebo-controlled trial in 47 patients with type 2 diabetes, administration of dapagliflozin 5, 25 or 100 mg once daily for 14 days alone or with metformin was well tolerated and no changes in body weight, urine volume or urinary sodium excretion were detected. The efficacy results of this study are discussed in the following section. Adverse events were observed in 20 of 39 patients given dapagliflozin, while 7 of 8 patients given placebo experienced adverse events. There were 37 and 19 adverse events, respectively, in the dapagliflozin- and placebo-treated patients. Most adverse events were of mild to moderate intensity, apart from a severe case of constipation and a severe case of flank pain, both in patients taking metformin (26, 27).

Dapagliflozin doses of 2.5, 5, 10, 20 and 50 mg were compared to metformin and placebo in a study in 329 diabetes patients. In this randomized, double-blind trial, 12 weeks of treatment with dapagliflozin was safe, with urinary tract infection, nausea, dizziness, headache, fatigue, back pain and nasopharyngitis being the most common adverse events seen with the drug. While the rate of hypoglycemic events was higher than in the placebo group, it was similar to the metformin group and no hypoglycemic events with a documented glucose level of 50 mg/dl or below were observed. No clinically meaningful changes in serum sodium, potassium or creatinine or in serum or urinary calcium were seen. Increases from baseline in mean serum magnesium of 0.1-0.2 mEq/l were seen with dapagliflozin across all doses by week 12, and an increase in mean serum phosphate of 0.2 mg/dl was seen with the highest doses. A decline in serum uric acid was also observed with dapagliflozin (28).

Clinical Studies

Pharmacodynamic analysis in the above-mentioned study in healthy volunteers indicated that doses above 20 mg provided maximal inhibition of renal glucose reabsorption, with cumulative 24-h urine glucose excretion with 2.5 and 10 mg dapagliflozin approximately 50% and 70%, respectively, of excretion after the higher doses. Daily urinary glucose excretion was similar after the first dose and after 14 days of dapagliflozin administration (24).

Two double-blind clinical studies represent what should be the beginning of a steady flow of clinical data concerning the effects of dapagliflozin in patients with type 2 diabetes.

In one trial, 47 patients who were drug-naïve or on stable doses of metformin for at least 4 weeks were randomized to placebo or dapagliflozin 5, 25 or 100 mg once daily for 14 days. Drug exposure was proportional to dose, and the mean amount of glucose eliminated in urine over 24 h after the first dose also increased with dapagliflozin dose: 45.2, 75.3 and 81.3 g, respectively, with 5, 25 and 100 mg. Daily glucose excretion was stable over the course of the study, although inhibition of glucose reabsorption was somewhat greater after 14 days than after the first dose. On day 14, the mean inhibition of renal glucose reabsorption (0-4 h) was 0.88%, 19.77%, 40.88% and 44.01%, respectively, for placebo and dapagliflozin 5, 25 and 100 mg. Fasting serum glucose was decreased significantly by each dose by day 13 compared to day –2 (14.5-21.9%), as was the 75-g oral glucose tolerance test $AUC_{0\text{-}4h}$ (18.8-22.9%) (26, 27).

The second study was larger, including 389 treatment-naïve patients with type 2 diabetes, and longer, lasting 12 weeks. Patients were randomized to placebo, extended-release metformin (metformin XR) 750 titrated to 1500 mg, or dapagliflozin 2.5, 5, 10, 20 or 50 mg given once daily. All dapagliflozin doses were associated with improved glycemic control compared to placebo, with mean reductions in HbA1c from baseline to week 12 of 0.71%, 0.72%, 0.85%, 0.55% and 0.90%, respectively, with dapagliflozin 2.5, 5, 10, 20 and 50 mg (all $P < 0.01$ *vs.* placebo). Fasting plasma glucose was reduced by 16.2, 19.3, 21.1, 24.4 and 30.5 mg/dl in these groups, respectively, at week 12. Postprandial glucose, measured by 3-h 75-g oral glucose tolerance testing, was reduced 9382, 8478, 10,149, 7053 and 10,093 mg.min/dl, respectively, in the dapagliflozin 2.5, 5, 10, 20 and 50 mg groups at week 12. Insulin concentrations were not increased (28).

A number of phase I-III clinical trials are under way evaluating the efficacy, safety and pharmacokinetics/pharmacodynamics of dapagliflozin both alone and in combination with other agents (29-40).

Sources

Bristol-Myers Squibb; codeveloped with AstraZeneca.

Online links

Subscribers to Prous Science Integrity® can access an online animation (Renal Sodium Glucose Cotransporters: Mechanism of Action) describing sodium-glucose cotransport.

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