

Section: Overview

Pharmacoepidemiology of Diabetes

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The Epidemiology of Antidiabetic Drugs

Type 1 Diabetes

Type 1 diabetes requires insulin treatment soon after diagnosis and thereafter insulin must be continued life-long without interruption. By some definitions type 1 diabetes may have shorter or longer periods early in the disease during which insulin is not yet needed. Insulin secretagogues are often used in such cases before the diagnosis becomes clear, but they will eventually fail to control hyperglycaemia as marked insulin deficiency becomes established. Furthermore, as the obesity epidemic also strikes in patients with type 1 diabetes, combinations of classical insulin treatment regimens with insulin sensitizers, metformin, and in some countries, thiazolidinediones, are becoming more common. Nonetheless, for the 5–10% of the world's diagnosed diabetics who have type 1 diabetes, insulin monotherapy remains lifesaving therapy. The prevalence of type 1 diabetes varies enormously with population genetics, a subject that has been thoroughly discussed elsewhere. Within the seven major insulin markets (USA, Japan, France, Germany, Italy, Spain, UK – total sales) the prevalence of type 1 diabetes ranges from 0.2% (Japan) to 0.7% (Germany). In these countries alone, more than 3.1 million (with an expected increase to

3.4 million in 2011) people are affected. Even though insulin treatment is mandatory, a number of issues cause continued concern from a pharmacoepidemiological viewpoint.

Availability of Insulin

Unfortunately insulin, even in standard formulations (porcine, bovine or human insulin in vials for subcutaneous injections), is not necessarily accessible to all patients with type 1 diabetes. In a survey by the International Diabetes Federation (IDF) Task Force on Insulin performed in 2003 [1], only 44 and 40 out of 74 responding countries reported uninterrupted access to insulin for people with type 1 or type 2 diabetes, respectively. Thus, in 30 countries, people with type 1 diabetes were without continuous access to insulin. Cost remains a major cause of lack of access. However, availability, transportation problems and poor quality of insulin were also reported as major issues. There are considerable regional differences with African countries reporting the worst situation. An unfortunate consequence of low access to insulin is pressure on health personnel and authorities to give preference to people with type 1 diabetes over people with type 2 diabetes. However, as highlighted recently by Beran and Yudkin [2] the life expectancy of patients with type 1 diabetes in parts of sub-Saharan Africa remains extremely short. This situation has changed little in some countries over the last decade. On a global basis, the commonest cause of death in a child with diabetes eight decades since the discovery of insulin is lack of access to the drug. The recent decision by

NovoNordisk to make insulin available to 50 of the world's poorest counties at no more than 20% of the average price in Europe, North America and Japan has been applauded [3]. However, the impact of this initiative has so far been limited.

New Insulin Formulations

In many countries, animal insulin in vials remains the cheapest and most accessible form of insulin, although in North America human insulin is now the cheaper option. The paradigms for insulin treatment have changed within the last two decades with the introduction of insulin analogues and, to a certain extent, increasing use of insulin pumps as an alternative to subcutaneous injections. Currently a new change is emerging, namely the use of non-injection insulins, with inhaled insulins becoming available in some countries [4]. In contrast to the situation in type 2 diabetes, there is as yet no convincing evidence for insulin treatment during the pre-diabetes phase of type 1 diabetes. The market therefore reflects the prevalence and availability of insulin and, unfortunately, health economy politics including reimbursement policies.

The Global Insulin Market

Sales of rapid-acting analogues of insulin now exceed those for human sequence insulin. Humalog and Novolog (Novorapid) had combined sales totalling US\$1555.2 million in 2005 compared with US\$870.2 million for all other rapid-acting insulins, Humalog being the market leader. The intermediate-acting insulins, Humulin and Novolin (Insulatard) being the dominant examples, sold US\$1050.8 million in 2005, which was a small decrease compared with 2004. The market (US\$1576.8 million in 2005) for prolonged-duration analogues is dominated by Lantus, with Levemir gaining some ground since its introduction. All insulins, including premixed formulations with a sale of US\$2256.1 million in 2005 and dominated by Novolog Mix, Novolin Mix and Humalog Mix, are used for both type 1 and type 2 diabetes (all data from [5]). As a consequence there has been a general increase in the use of insulin. Data from recent years in Denmark (with an estimated 25,000 patients with type 1 diabetes and more than 200,000 patients with type 2 diabetes) are shown in Fig. 1. Data from France [6] showed a

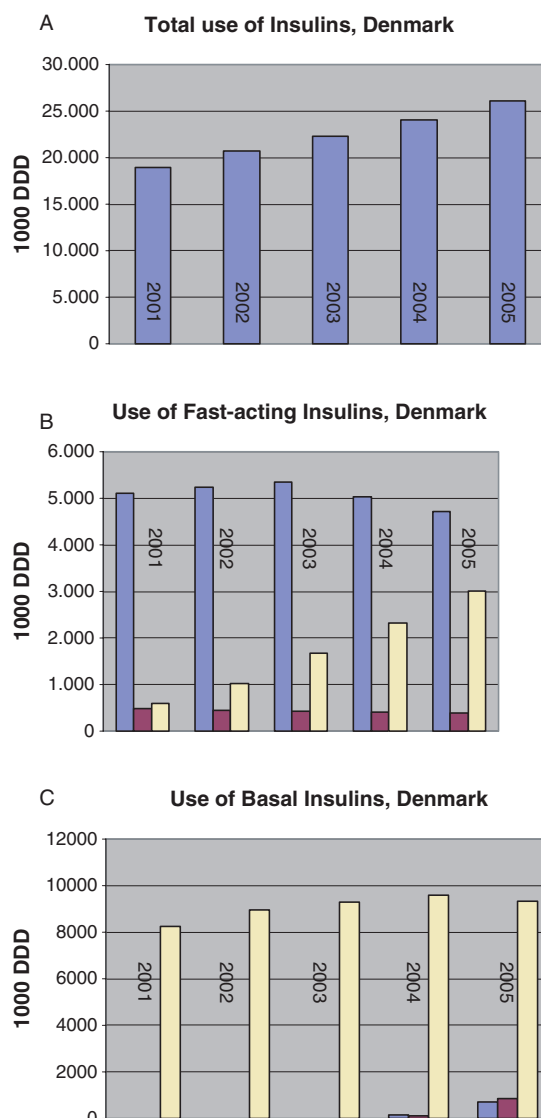


FIG. 1. Trends in the use of insulin in Denmark in the new millennium, all insulins (defined daily doses, DDD) (A), fast-acting insulins (left human insulin, middle lispro, right aspart) (B), basal insulins (left glargine, middle detemir, right human insulin) (C). (From The Danish Medicines Agency at www.dkma.dk.) The numbers reflect the use of insulin in 44,467 patients in 2001, increasing to 56,501 in 2005. Total use of analogues is increasing.

tripling of the use of insulin from 1976 to 1989 most likely driven by the increasing burden of type 2 diabetes. In addition, the adjuvant use of novel amylinomimetics has gained some ground in the USA.

Prescribing of Insulin in Type 1 Diabetes

Internationally, guidelines for the treatment of type 1 diabetes vary little between countries. In essence, the goal remains near-normal glucose levels without inducing severe hypoglycaemia. The options available are legion although the intrinsic limitations of subcutaneous insulin delivery continue to act as a barrier to attainment of this goal in the majority of patients. Although some regimens appear to offer certain advantages over others [7], the choice of treatment remains dependent on the availability of insulin preparations (and delivery systems), local professional expertise and provision of support, and individual preferences of both patients and the diabetes healthcare team. As stated above, while paradigms of care may change, the choice of therapy often reflects the impact of factors other than evidence for treatment efficacy (and safety). For example, in otherwise comparable markets (Denmark and Sweden), the use of continuous subcutaneous infusion systems varies significantly [8] according to reimbursement policies.

Type 2 Diabetes

In the majority of subjects type 2 diabetes is usually not well controlled by lifestyle modifications and so presents major challenges to pharmacotherapy. The increasing number of ways to attack the cardinal metabolic defects of type 2 diabetes – insulin resistance and beta-cell failure – leaves patients and doctors with numerous possibilities for pharmacological interventions. The forecast of increased prevalence of diabetes in the coming years raises enormous ethical and practical questions, which must be resolved to supply patients with the necessary drugs. Data from the IDF suggest that overweight and obesity will affect major proportions of the population in the USA and large European countries, with France at 36% and the USA at 51.9% [1] by 2011, the latter increasing from 45.5% in 2005. Unless this trend is reversed, which at the moment appears unlikely, type 2 diabetes will affect significant proportions of the population. In 2005, Italy registered 6.2% of its population as having type 2 diabetes (increasing from 6.0% in 2004); corresponding figures from the USA were 6.1% and 5.9%. In the USA,

diabetes mortality increased from approximately 68,000 deaths in 1999 to 74,000 deaths in 2003. Diabetes is the sixth leading recorded cause of death in the USA [5].

Availability

Varying with socioeconomics and health policies, the availability of oral or injectable antidiabetic agents varies. However, basic drugs for beta-cell stimulation, the sulphonylureas, and for treating insulin resistance and increased hepatic glucose output (the biguanides) remain cheap, effective and widely accessible. Alpha-glucose inhibitors and, in particular, thiazolidinediones, retarding the rates of intestinal glucose absorption and tissue insulin resistance, respectively, are alternatives that have been increasing in use and availability.

The Market for Antidiabetic Agents for Type 2 Diabetes

Including insulin, half of the global diabetes market is accounted for by the USA. Other major markets are Germany (7%), the UK (4%) and France (3%). Highly populated countries with substantial numbers of people with diabetes such as Russia and Brazil each account for approximately 1% of the market. The market is dominated by (54%) original branded drugs; however, generics account for some of the market and unknown numbers of patients are treated with “generics” in countries such as China and India where licensing regulations are less strict [5]. Oral antidiabetic drugs account for 58% of the total market worth US\$18.6 billion in 2005, an increase of 11.5% compared with 2004. The market is led by the thiazolidinediones with a pioglitazone turn-over worth US\$ 2.544 billion in 2005 (rosiglitazone US\$ 2.258 billion, rosiglitazone/metformin combination US\$ 382.7 million, metformin US\$ 518.7 million, glimepiride US\$ 857.9 million, voglibose US\$ 547.1 million). There are few descriptions of regional differences in prescription patterns. It can only be assumed that, as for insulin, availability varies and expectedly even more so since several oral antidiabetics can be used to achieve the same treatment goals in the individual patient. When drugs for associated conditions are included, it is likely that for some

high-prevalence countries, Germany, for example [9], diabetes may account for more than 20% of total pharmacy costs; cardiovascular drugs are the most important cost factor, reflecting the rates of atherosclerotic complications.

Prescribing of Antidiabetic Drugs for Type 2 Diabetes

Although hard end-point studies are somewhat sparse in diabetology, little doubt exists that near-normal blood glucose levels are beneficial, relieving symptoms and preventing long-term vascular complications. Guidelines are legion, and treatment goals are becoming increasingly ambitious. For example, the latest IDF guidelines for the treatment of type 2 diabetes [10] aim for HbA_{1c} levels lower than 6.5%. Since this goal is rarely achieved through lifestyle measures alone, oral antidiabetic agents are usually required. Initially, monotherapy is commenced with the most appropriate drug, based on the clinical and biochemical profile of the patient, and in the light of safety considerations. For most patients, drugs from different classes are required in varying combinations, insulin being ultimately necessary in many patients. Current guidelines recommend metformin and sulphonylureas as first-line therapy.

Other regimens may be equally effective or even more so. However, comparative studies are sparse. With very prevalent diseases such as type 2 diabetes, pharmacoeconomics become extremely important. Thus, both the economy of society at large and the economy of the individual patient must be taken into account when choosing drug therapy. Safety issues remain important since treatment will often be continued for many years or even life-long, during which time complications, for example, nephropathy or cardiovascular disease, that may alter the safety profile of certain drugs may develop.

Trends in the Use of Antidiabetic Drugs

A recent survey [11] of antihyperglycaemic drugs in ten European countries showed that their use increased in all countries but with very different treatment patterns. The use of insulin doubled from 1994 to 2003 in some countries (England and Germany) but remained stable in others (Belgium, Portugal, Italy). The use of biguanides increased substantially, whereas the use of sulphonylureas increased more moderately in most countries. Insulin accounted for more than 50% of the daily antidiabetic doses in Sweden, the corresponding number in Portugal was <20% (Fig. 2). In an

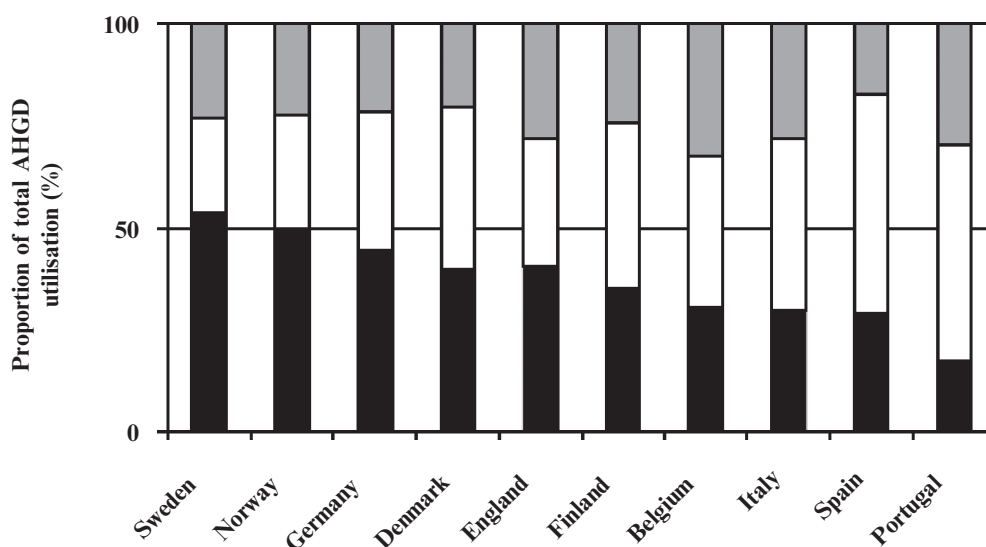


FIG. 2. Use of insulins (black), sulphonylureas (white) and biguanides (grey) as proportions of the total use of antidiabetic drugs in ten European countries (2003). Regional variation is substantial. Reproduced with permission from [11].

interesting comparison between Finland and Denmark (with the expected prevalence of diabetes being 7.2% and 6.9% in 2003, respectively) it was found that in 2000, 3.15% of the population in Finland (insulin 1.76%, oral agents 2.40%) was treated with antidiabetic drugs, the corresponding numbers for Denmark was 1.96% for any antidiabetic treatment (insulin 0.78%, oral agents 1.31%) [11]. It is unlikely that differences in detection levels of diabetes or different diabetic phenotypes, let alone drug availability, can explain such a difference. Local therapeutic convention is a plausible explanation. As described in a comparison of two neighbouring communities in Sweden [12] tradition (specialized diabetes clinician compared with non-specialist clinicians) may have major influences on both drug type and dose. Along with progressively more aggressive treatment of glycaemia, the use of cardiovascular and lipid-lowering drugs also increases with time in patients with diabetes [13]. Although the result is improvements in a number of biochemical risk factors, the relation between prescriptions and improved survival remains somewhat elusive since time-related changes are severely confounded by improved diagnostic awareness and, particularly in the case of diabetes, of recent changes in diagnostic levels of blood glucose [14].

The impact of recommendations or guidelines (more similar between countries for cardiovascular diseases) has been studied in the Euroaspire programme [15]. Among patients with coronary heart disease there appears to be room for improvement in aspects of cardiovascular prescribing if international guidelines were to be rigorously applied. For antidiabetic drugs, however, it has been shown that changes in recommendations coincide with substantial changes in drug prescription [16].

Use of drugs to prevent diabetes or to treat related diagnoses (e.g. polycystic ovary syndrome) may result in changes in prescription patterns in the future. Such changes may confound the interpretation of data on drug use. At present there is some evidence for the efficacy of metformin, troglitazone (now withdrawn), orlistat, rosiglitazone and rimonabant [17–19] on delaying the development from impaired glucose tolerance to diabetes. However, use of these drugs to prevent diabetes is not currently recommended.

Pharmacoepidemiology of Diabetes: Safety Considerations

While phase 1 and 2 trials are necessary for the demonstration of early safety in humans, phase 3 trials (randomized controlled trials) are unsurpassed in design for the demonstration of the effects of a drug on the disease course (efficacy). Post-marketing phase 4 trials vary in design; however, they are often not suited to evaluate therapeutic effects (effectiveness) in the population as a whole and long-term safety in non-selected groups of patients. Pharmacoepidemiology offers methods, retrospective but often including prospective follow-up designs, that allow for the surveillance of larger populations for longer periods. In many cases, as has recently been described for glargine, a long-acting insulin analogue, efficacy and effectiveness measurements are comparable in type and magnitude [20]. Unfortunately, safety issues have in some cases been undetected, and to some extent overlooked, as was the case for troglitazone in the late 1990s [21,22]. It should be borne in mind that well-established antidiabetic drugs such as metformin, sulphonylureas and insulin, even when used appropriately, are associated with appreciable rates of morbidity and, less frequently, mortality [23].

Diabetes-related pharmacoepidemiological research, applying state-of-the-art methodologies, may prove to be a helpful tool in choosing which drugs to prescribe. Recently we [24, 25] and others [26] have evaluated the safety of sulphonylureas by epidemiological methods. Based on preclinical evidence it was suspected that some sulphonylureas were preferable to others with respect to the main cause of mortality in type 2 diabetes, myocardial infarction. In population-based studies from Italy and Denmark similar results have shown a significantly reduced risk of myocardial infarction and mortality (relative risks being approximately 0.8) for gliclazide and glimiperide when compared with other sulphonylureas. This applies for monotherapy as well as for combination therapy when sulphonylureas are used together with antidiabetic agents from other classes. The results were unchanged by corrections for a large number of potential confounding factors, a key issue in epidemiological research that can now be met with an increasing use of detailed databases that allow simultaneous registrations of treatment, disease and

mortality data and a large number of socioeconomic parameters. The estimated number of participants in a prospective controlled trial designed to test this hypothesis would be >60,000 for a 5-year period making the performance of such a study less than likely on economic and practical grounds.

Thus, structured epidemiological surveillance of established diabetes treatments can powerfully complement more established methods used during the development of new drugs.

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