Biosimilar medicines and their use: the nurse's role and responsibility

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Abstract

Nurses have a central role in the delivery of medicine and education of patients; however, training for nurses on new products is often ad hoc and incomplete. As a result, nurses may be unaware of the complexities and consequences of using new therapeutic protein drugs such as biosimilars. Unlike small-molecule generic drugs, biosimilars are biopharmaceuticals which are similar, but not identical, to the innovator biopharmaceutical products they seek to replicate. With the advent of these medicinal products, nurses face new challenges in their role in patient care. Poor knowledge of biosimilar medications could result in serious medication errors, adverse events or a delay in desired therapeutic gain for the patient. Pharmaceutical education of healthcare providers is paramount to ensure patient safety as biosimilars are introduced into clinical practice. This article discusses these challenges and the need for increased awareness of biosimilars in nursing and clinical practice.

Key Words

Biosimilars, biopharmaceuticals, nursing

Introduction

Nurses have important roles in the pharmaceutical therapy a patient receives. Despite this, no regulated ongoing education in relation to pharmaceutical products, including biopharmaceuticals, is routinely targeted at nurses. The advent of biosimilars and a lack of knowledge concerning these products highlight the low importance placed on continuing pharmaceutical education.

Biopharmaceuticals are medicinal biotechnology drug products that have been on the market since the 1980s and used to treat chronic and often debilitating diseases, such as anaemia, certain cancers, haemophilia, and diabetes. Such drugs include blood factors, hormones, cytokines, hematopoietic growth factors (Schellekens, 2005; Covic and Kuhlmann, 2007). The patents of several first-generation biopharmaceuticals have expired in recent years or will be expiring in the near future (Schellekens, 2004). Expiration of these patents has provided an incentive for manufactures to develop new versions of these products, called biosimilars or follow-on biopharmaceuticals, and consequently, there are now an increased number of medicinal proteins available to treat patients.

Nurses are accustomed to administering generic versions of chemically synthesised drugs which exhibit identical therapeutic properties and adverse events as their branded counterparts. Biosimilars, however, are not identical to innovator biopharmaceutical products they seek to replicate. The lack of nursing awareness and education about biosimilars can lead to medication errors, adverse events or a delay in desired therapeutic gain for the patient. This article presents the challenges faced by nurses in their role and responsibilities in the management of patients receiving biopharmaceutical therapy. Also discussed are the challenges presented by biopharmaceuticals and the need for greater vigilance by nurses which will be achieved through constructive ongoing pharmaceutical education.

Challenges to the nurses' role in pharmaceutical therapy

Nurse training on pharmaceuticals is based on an understanding of their application in the treatment of patients. Nurses are not formally educated in analytical and critical thinking processes that result in a pharmaceutical prescription. Critical thinking skills in relation to pharmacology are more

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likely acquired through experience and empirical knowledge. Several challenges exist in the nurses' pharmaceutical role. The first challenge is the prevention of errors during delivery of care, and, the second challenge is evaluating the therapeutic benefit of the current medication regimen. Problems that can contribute to medication errors include lack of pharmaceutical knowledge and complacency with new pharmaceutical products. In many nursing practices, there are no consistent or comprehensive means by which nurses are kept abreast with latest advances in marketed medicines. It is not uncommon to find infrequent access to formal and informal ongoing education regarding pharmacological advances or changes, and evidence-based information for new products. In addition, few pharmaceutical companies engage nurses in product education; such information is often tailored for prescribers. Often the onus is on the nurse to seek out pharmaceutical product information. This is frequently limited to reference books or similar publications, which may be biased and not be current. Computer access, if at all available, is often limited to intranet resources, which may not be comprehensive. With many biopharmaceutical products available, the nephrology nurse may be administering several drugs to a single patient, highlighting the need for vigilance in relation to knowledge.

The consequence of this lack of ongoing pharmaceutical education is decreased knowledge of safety and efficacy of drug groups. This is of concern as nurses in many cases are responsible for administering or supervising the patient's pharmacological regimen, providing patients with pharmaceutical information and safety instructions, and for observing both the beneficial and adverse response to therapy. This is made more complex in the case where patients suffer from, and are being treated for, multiple comorbid conditions. For example, the nephrology nurse not only monitors the care of the patient in the dialysis centre, their response to the dialysis prescription, but also monitors the comorbidities and complications of kidney disease such as anaemia. For kidney disease patients with anaemia, the nephrology nurse must ensure the patients receiving a correct (as prescribed) and adequate dose of erythropoiesis-stimulating agent (ESA), a biopharmaceutical product, to achieve optimal haemoglobin targets.

In most cases, a nurse's knowledge of the benefits and adverse events of a pharmaceutical agent is acquired through experience and observation. For small molecule pharmaceuticals, generics have the same qualitative and quantitative active properties (i.e. bioequivalent) as their innovator counterparts (EMEA, 2001; FDA, 2010); therefore, a nurse may have more experience and confidence in interchanging one medication with another, and/or assess adverse events the drug is expected to induce. However, the danger of such practice is that it may lead to complacency, as it is assumed that all pharmaceutical products used for the same condition will exhibit identical therapeutic properties with predictable adverse events and no anticipated differences from one brand to another (Baker, 1988). However, as mentioned, biosimilars are not generic forms of innovator biopharmaceuticals, so this may translate to expectations of evaluating therapeutic gain or assessing adverse events when a patient's medication is changed from one biopharmaceutical to another. The advent of biosimilars has added a new dimension to a nurse's role and responsibilities in caring for patients.

What is a biosimilar and what makes it different?

Unlike chemical-based pharmaceuticals, most of which are small molecules with a relatively simple homogenous structure, biopharmaceuticals are large, highly complex, heterogeneous molecules (Roger, 2006; Schellekens, 2005). The structural complexity of biopharmaceuticals and the intricate biological process required to manufacture them, means that two biopharmaceuticals intended to be similar can never be identical (Roger, 2006; Schellekens, 2005). Some of the differences between chemical-based drugs and biopharmaceuticals are summarised in Table 1.

Table 1. Differences between chemical-based pharmaceuticals drugs and biopharmaceuticals

Chemical-based Pharmaceuticals (Rader, 2008)	Biopharmaceuticals (Rader 2008; Schellekens, 2004)
Small, simple and well defined structure	Large, complex, heterogeneous structure
Easily characterised - purity and content can generally be analysed and demonstrated	Difficult to characterise - properties are dependent on the manufacturing process
Well-defined, simple manufacturing process	Complex manufacturing process
Relatively stable	Relatively unstable

In contrast to the relatively simple manufacturing method of chemical-based pharmaceuticals, biopharmaceuticals have a complex method of manufacture, which involves many different steps (Chirino and Mire-Sluis, 2004). The properties of biopharmaceuticals are dependent on the manufacturing process, which include the cell expression system, cell culture and growth conditions, and the extraction/purification processes (Molowa and Mazanet, 2003). Disparity in the production process between a biosimilar manufacturer and the innovator arises because the innovator company retains the proprietary details of the original manufacturing process for producing the biopharmaceutical and the manufacturer of the biosimilar product does not have access to them. In the absence of access to such proprietary information, each new manufacturer strives to emulate the originator's process as much as possible (Raines, 2002) whilst accepting that it will never be exactly the same. Therefore, as the process of copying highly complex biologically active proteins is difficult, the risk of introducing small changes to the protein product is high (Kresse, 2009).

One of the significant challenges in the production of biosimilars is the fact that changes in manufacturing processes that may seem inconsequential may have a major impact upon biological activity, and thus affect the efficacy and safety of the end product in a manner that is not easily measured using analytical techniques (Raines, 2002; Rossert, et al., 2004; Schellekens, 2002). Adding to the degree of uncertainty is the fact that the biological and clinical properties of biopharmaceuticals cannot be completely predicted by laboratory based measure alone. Despite the fact that a biosimilar manufacturer ensures consistency in the production process and applies stringent quality control of the end product, this process, however rigorous, will not guarantee that the clinical characteristics are exactly the same as those of the innovator biopharmaceutical.

The challenges of biosimilars in clinical practice

As noted, biosimilars are not identical to the innovator and are therefore not generic versions of innovator products, and there is limited clinical experience of these new products at approval. Structural differences between the biosimilar and innovator product may affect clinical outcomes. In Australia, the Therapeutic Goods Administration (TGA) has adopted the European Medicines Agency's (EMA's) guidelines for assessing biosimilars and requires a degree of clinical testing, to exclude differences in safety, efficacy and immunogenic potential, before approval (TGA, 2009). These studies will be less extensive than those conducted by the innovator company before approval of the original biopharmaceutical. However, despite this clinical testing before approval, differences between biosimilars and innovators, with respect to efficacy and safety may not become apparent during the pre-approval period, as only a limited number of patients will have received the product over a limited time-span. Therefore, it is important to monitor initial and short term individual responses as well as post-marketing pharmacovigilance (EMEA, 2005; TGA, 2009).

It is also important to note that as biosimilar products are approved for marketing in Australia, there may be significant post-marketing commitments that will have to be taken into account by medical staff. An important aspect of this post-approval data collection may be hampered by the ability to distinguish between different biosimilar and reference products. Differentiating one biopharmaceutical from another is complicated by the fact that to date, some biosimilars have been given the same International Non-proprietary Name (INN). Identification of the different biopharmaceutical products can therefore only be achieved via their brand names.

The assignment of the same or similar INNs to different biosimilars can be illustrated by the recent approval of erythropoiesis-stimulating agents

Table 2. Recombinant erythropoietins developed as biosimilars to Eprex® and approved in the European Union for treatment of anaemia in chronic renal failure

Product	INN	Authorised	Marketing Authorization Holder
Binocrit®	epoetin alfa	2007	Sandoz GmbH, Germany
Epoetin alfa Hexal®	epoetin alfa	2007	Hexal Biotech Forschungs GmbH, Germany
Abseamed®	epoetin alfa	2007	Medice Arzneimittel Putter GMBH & Co, Germany
Retacrit®	epoetin zeta	2007	HOSPIRA Enterprises, The Netherlands
Silapo®	epoetin zeta	2007	STADA Arzneimittel AG, Germany

(ESAs) by the Committee for Medicinal Products for Human Use (CHMP) of the EMA. ESAs are used in the treatment of anaemia in patients with chronic kidney disease. In Europe, the innovator product, Eprex® (Epoetin alfa, Janssen-Ortho Inc, Canada), has been available for several years. Binocrit® (Sandoz GMbH, Holzkirchen, Germany), also marketed as Epoetin alfa Hexal® (Hexal Biotech Forschungs GmbH, Holzkirchen, Germany), and Abseamed® (Medice Arzneimittel Putter GMBH & Co, Iserlohn, Germany), are biosimilar to Eprex®. Like Eprex®, all three biosimilars are intended for the treatment of anaemia in chronic renal disease (EMEA, 2007). Although slight structural differences exist between the drugs (Binocrit EPAR Summary, Epoetin alfa Hexal EPAR Summary, Abseamed EPAR Summary), the same INN (epoetin alfa) is used for all these ESAs. Other biosimilar erythropoietins, used to treat the same condition, are also available in Europe (see Table 2). In Australia, currently, only Eprex®, NeoRecormon® (Epoetin beta, Hoffman-La Roche Ltd, Switzerland), and Aranesp® (Amgen Inc., U.S.A.) are the three ESAs approved for the treatment of anaemia associated with chronic renal failure and with treatment of certain malignancies.

Having the same name for biopharmaceutical products can lead to the presumption that they are identical to each other. Given that it is commonplace in medical practice to use the INN as a means of identifying chemical drugs that are identical to one another, as is the case with generic medicines, this could result in automatic substitution whereby patients can be switched from one product to another when a prescription is dispensed without the knowledge of the treating physician, patient, or nursing staff (Nowicki, 2007). Without knowledge of such a change in medication by medical staff, this situation makes pharmacovigilance particularly difficult; if care is not taken to clearly identify the precise agent by using the brand name, it would be impossible to track the specific agent that may cause an adverse event, and subsequently makes it difficult to effectively monitor safety of the ESA class. Recognizing this problem, several European countries have taken steps to limit automatic substitution of such products (Pavlovic, et al., 2008; MHRA, 2008). The EMA's opinion on biosimilar medicines states "Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional" (EMEA, 2008). Within Australia, following the European model, a biopharmaceutical is dispensed without substitution. However, there is the potential for errors in nomenclature and charting of medication, so substitution with a biosimilar is not an unlikely scenario. Compromised patient safety exists if the nurse is unfamiliar with problems of substitution.

The nurses' responsibility in biosimilar therapy

The challenges posed by biosimilar products have important implications for the nursing practice. Biosimilars require special consideration when designing educational curriculum or materials, advising patients and colleagues, assessing medication substitution, and assessing and evaluating patients. These challenges require the nurses engage in a proactive role in being well informed about biopharmaceuticals that are available, and gain knowledge and training that is current and evidence-based.

In addition to education, it is essential that nurses take meticulous records when administering biopharmaceuticals. The use of biosimilars is essentially a change in clinical management (Mellstedt et al., 2008). Whether a biosimilar or an innovator medication is prescribed, it needs to be charted correctly, and include not just the INN class but the brand name. Meticulous records and patient evaluation allows for better evaluation of therapeutic benefits and assessment of adverse events during treatment, and reduces the risk of medication errors.

In many cases, a nurse's skills and knowledge goes beyond just educating, mentoring and influencing others in the same profession, and has an impact on safe medical practice. A nurse's expertise is often sought from primary health care providers. In practices such as nephrology, nurses have significant influence by providing advice to junior medical officers and general practitioners with lesser knowledge of medication dosage in patients with kidney disease. It is therefore important that nurses know and understand the use and effects of drugs, including understanding any special requirements or differences in requirements for innovator and biosimilar products. In addition to understanding the use and effects of biopharmaceuticals, the nursing profession needs to develop standard policies and procedures to optimise their safe use.

As in any other medical regimens, patients need to be consented and informed about their treatment and potential adverse events. Keeping patients informed is paramount to the successful management of chronic diseases like kidney disease, which rely heavily on self-management by the patient. Patients who are well informed are able to better partner with their healthcare providers in optimizing their treatment.

Figure 1.

Take Away Points

- Nurses must be aware that biosimilars and innovator biopharmaceuticals are not identical. Unlike small-molecule drugs, these medicinal proteins cannot be interchanged.
- The complex nature of biopharmaceuticals requires that nurses are better informed about their differences (to the extent they exist), use and effects, as well as exercise greater prudence in monitoring patient safety when one product is switched for another.
- To have this greater awareness, nurses must play a proactive role in being well informed about biopharmaceuticals that are available, and gain knowledge and training that is current and evidence-based.

Conclusion

The complex nature of innovator and biosimilar biopharmaceuticals requires that nurses are better informed about their differences (to the extent they exist), use and effects. Responsibility must be placed on manufacturers, professional bodies and prescribers to ensure the nursing profession has continuing access to updated information on current and emerging biopharmaceutical products. Safe use of such products should be embedded in education, policies, and procedures.

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