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Impact of new efficacy information on sales of antihypertensive medicines in Japan and Sweden

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ABSTRACT

Objectives: The generic substitution of medicines has been introduced in Europe since the 1990s to increase price competition and the use of cheaper equivalents. Patent expiry is assumed to be associated with changes in sales patterns, particularly when combined with generic substitution. Other changes have been observed when prescribers obtain new information on drug safety and efficacy of medicines. This article examines to what extent patent expiry and new medical information on efficacy influence the pharmaceutical sales patterns of antihypertensive medicines in Japan and Sweden.

Methods: Angiotensin-converting enzyme inhibitors and angiotensin II antagonists (ARBs) were selected, since they are widely used in both Japan and Sweden. The two analysed interventions were patent expiry and published information on lower efficacy for two ARBs. Seasonal autoregressive integrated moving average modelling with intervention was used to analyse changes in sales volumes.

Results: Patent expiry was not associated with any significant changes in sales patterns. In Sweden, the sales rate of losartan increased following new information on lower efficacy for candesartan and telmisartan (0.77650 DDDs/1,000 inhabitants per day, $p = 0.0068$), whereas candesartan sales decreased (-0.50760 DDDs/1000 inhabitants per day, $p = 0.0058$). In Japan, the publication of new efficacy information was also associated with a significant decrease in candesartan (−1.21215 DDDs/1000 inhabitants per day, $p = 0.001$).

Conclusions: We found sales patterns of antihypertensive medicines were to a large extent affected by information on efficacy rather than patent expiry. However, further assessment is needed for other medicine groups and settings. (248 words)

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Introduction

Generic substitution was introduced in several European countries in the 1990s to increase price competition and the use of cheaper equivalents [1]. In some countries, such as Germany and Sweden, the increasing pharmaceutical expenditure levelled off or decreased following various policy changes [2,3]. Previous studies reported generic substitution was associated with lower brand name drug prices [4]. Under generic substitution, pharmacies are allowed to switch from brand name to equivalent generic drugs, with lower prices once the patent of the brand name product expires. Therefore, generic substitution should theoretically facilitate changes in sales patterns related to patent expiry. Generally, the share of brand name drugs decreases at the time of patent expiry, while the share of generic drugs increases [5]. Other interventions, such as therapeutic substitution, substitution of off-patent with in-patent drugs within the same therapeutic drug group, and use of fixed-dose combinations, have also been reported to impact sales. However, there is no evidence on their impact on rational drug use. Therapeutic substitution may affect the impact of generic substitution. For instance, a previous study reported therapeutic substitution was associated with a negative impact on the

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Table 1
Decription of the type of substance, patent expiry and release of new information for the selected drugs in Sweden and Japan.

ATC-code	Substance name	Japan				Sweden			
		Category	Sales year	Substitutable since	New efficacy information	Category	Sales year	Substitutable since	New efficacy information
C09AA01	Captopril	NP	1983.02	1997.07	–	NP	1982.04	2002.10	–
C09AA02	Enalapril	NP	1986.07	2000.07	–	NP	1985.09	2002.10	–
C09AA03	Lisinopril	NP	1991.08	2000.07	–	NP	1988.10	2002.10	–
C09AA04	Perindopril	PE	1998.04	2005.07	–	–	1998.11	–	–
C09AA05	Ramipril	–	–	–	–	PE	1991.05	2004.10	–
C09AA06	Quinapril	PP	1995.09	–	–	PE	1990.09	2007.09	–
C09AA07	Benazepril	PE	1993.04	2003.07	–	–	1990.12	–	–
C09AA08	Cilazapril	PE	1990.11	2004.07	–	–	1991.08	–	–
C09AA09	Fosinopril	–	–	–	–	PE	1996.10	2008.03	–
C09AA10	Trandolapril	PE	1996.05	2003.07	–		1997.04	–	–
C09AA12	Delapril	PP	1989.04	–	–	–	–	–	–
C09AA14	Temocapril	PE	1994.08	2009.05	–	–	–	–	–
C09AA15	Zofenopril	–	–	–	–		1999.03	–	–
C09AA16	Imidapril	PE	1993.12	2008.07	–	–	–	–	–
C09CA01	Losartan	PE	1998.08	2012.06	2011.04	PE	1994.09	2006.03	2010.10
C09CA02	Eprosartan	–	–	–		PP	1997.09	–	–
C09CA03	Valsartan	PP	2000.11	–	–	PE	2001.11	2008.11	–
C09CA04	Irbesartan	PP	2008.07	–	–	PE	1997.08	2007.08	–
C09CA06	Candesartan	PP	1999.06	–	2011.01	PE	1997.10	2008.11	2010.07
C09CA07	Telmisartan	PP	2005.01	–	2011.01	PE	1998.12	2008.11	2010.07
C09CA08	Olmesartan edoxomil	PP	2004.05	–	–	–	–	–	–
C09CA09	Azilsartan medoxomil	PP	2012.05	–	–	PP	2011.12	–	–

NP; No longer protected before study period, PE; Patent expire during study period, PP; Patent protected during study period.

implementation of generic substitution [6]. Following the introduction of generic substitution, there were fewer advertising activities and less information from brand name pharmaceutical companies for their products after patent expiry [6]. Changes in sales patterns have also been observed when prescribers receive information on drug safety and efficacy, for instance adverse drug events (ADEs), from which new evidence of therapies and/or cost-effectiveness is drawn [7]. Ohlsson et al. [7] reported a positive influence on statin prescriptions after the publication of official treatment guidelines. If the sales patterns change from off-patent to in-patent drug with the same substances, this might contribute to increased pharmaceutical expenditure. Changes in drug sales patterns are also related to national pharmaceutical policy changes, guided by both national and regional governing agencies in many countries. In this article, we examine to what extent patent expiry and new medical information on efficacy are related to the pharmaceutical sales patterns of two widely used groups of antihypertensive drugs in one country with voluntary generic substitution (Japan) and one with mandatory generic substitution (Sweden).

Methods

Study setting

We selected two groups of antihypertensive medicines, angiotensin-converting enzyme inhibitors, (ACE-inhibitors, Anatomical Therapeutic Chemical classification (ATC) code C09A) and angiotensin II antagonists (ARBs, ATC code C09C) that are recommended standard treatments with high sales volumes in Japan [8,9] and Sweden [10]. The study period ranged from 1 January 2002 to 31 December 2012 in Sweden and 1 January 2002 to 31 March 2013 in Japan.

Based on patent status, we classified the selected drugs into three categories as follows. Drugs no longer protected by patents before the study period were denoted as 'NP', drugs whose patents expired during the study period as 'PE', and drugs protected by patents during the study period as 'PP' (Table 1). To assess the impact on sales patterns over time due to patent expiry, only PE drugs were studied. To assess the potential impact of new information about drug safety and efficacy on sales patterns, we included three affected substances during the study period (losartan, ATC code C09AC01; candesartan, ATC code C09AC06; and telmisartan, ATC code C09AC07). The new information was based on two articles reporting candesartan and telmisartan did not have the expected renal outcomes from July 2009 [11,12]. These medicines also had a different status in relation to patent expiry.

Data

Aggregated sales data for the selected drugs in Sweden were collected from the Swedish eHealth Agency (e-hälsomyndigheten) and included medicines sold in pharmacies and hospitals. Sales data for selected drugs in Japan were collected from IMS Japan and included medicines sold to pharmacies, hospitals, and GPs by retailers. Quarterly data were collected and comprised volumes, expressed as defined daily doses (DDDs) per 1000 inhabitants per day [13]. We used census data for each year quarter for the population of both countries [14,15].

Statistical analysis

A time series analysis was conducted using seasonal autoregressive integrated moving average (ARIMA) modelling with intervention analysis. The ARIMA was based on the maximum likelihood method to estimate the effects of patent expiry and release of new information on the sales volume of the analysed drugs. Generally, an ARIMA model predicts a value in a response time series as a linear combination of its own past values, past errors, and current and past values of other time series. We used Box and Tiao's [16] study, which is based on Box and Jenkins' methodology, to determine the best matching ARIMA model with intervention. This approach has been used in several fields, such as health economics [17] and pharmacoepidemiology [18]. We selected one model for each time series: with a white noise pattern in residuals, with the least number of parameters, and minimum Akaike's information criterion (AIC). The outcome variables were sales volumes of selected drugs. Two interventions were analysed, with the

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