An investigation of prescription and over-the-counter supply of ophthalmic chloramphenicol in Wales in the five years following reclassification

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ABSTRACT

Purpose

The aims of the study were to (i) quantify the sales of over-the-counter (OTC) ophthalmic chloramphenicol from all community pharmacies in Wales and investigate the impact on primary care prescriptions up to five years after reclassification and (ii) investigate the temporal relationship between items supplied OTC and on NHS primary care prescriptions.

Methods

Primary care prescription data (2004-10) and OTC sales data (2005-10) for ophthalmic chloramphenicol were obtained. The quantity sold OTC was calculated from pharmacy wholesale records and sales data from a large pharmacy multiple. Spearman's rank correlation for prescription and OTC supplies of ophthalmic chloramphenicol was calculated for data from January 2008 to December 2010.

Results

OTC supply of chloramphenicol eye drops and ointment were both highest in 2007/08 and represented 68% (57,708/84,304) and 48% (22,875/47,192) of the corresponding prescription volume, respectively. There was a steady year-on-year increase in the combined supply of OTC ophthalmic chloramphenicol and that dispensed on prescription from 144,367 items in 2004/05 to 210,589 in 2007/08 before stabilizing in 2008/09 and 2009/10. A significant positive correlation was observed between prescription items and OTC sales of chloramphenicol eye drops and ointment combined ($r=0.7$, $p<0.001$).

Conclusion

OTC availability increased the total quantity of ophthalmic chloramphenicol supplied in primary care compared to that seen prior to reclassification. Although growth in the sales of ophthalmic chloramphenicol OTC has stabilised and the supply pattern mirrors primary care prescribers, further work is required to investigate if use is appropriate and whether the publication of updated practice guidance has changed this.

INTRODUCTION

Regulatory background

There are three categories for human medicines in the United Kingdom (UK), namely prescription-only medicines (POM), pharmacy-only (P) medicines and general sales list (GSL) medicines. POM medicines are only available on prescription, while P medicines can be sold from a pharmacy under the supervision of a pharmacist. In contrast, GSL medicines can be sold from most retail outlets.[1,2] Over-the-counter (OTC) medicines is a collective term used to describe P and/or GSL medicines that can be purchased without a prescription although in this paper it is used exclusively to indicate supply from a community pharmacy.

The main determinant of a medicine's legal status is its safety, although factors such as side effects, monitoring requirements, route of administration, liability to misuse and risk to human health are also considered.[2] When a medicine is 'switched' from one legal category to another this is termed reclassification. Reclassification from POM to P is associated with benefits for the patient[3,4,5], government[6,7,8], pharmacy profession[9] and drug industry.[10] Whether such reclassification is appropriate for an antimicrobial agent is unclear.

Ophthalmic chloramphenicol

Ophthalmic chloramphenicol was the first antibiotic available for purchase OTC in the UK and was indicated for the treatment of acute bacterial conjunctivitis. The eye drops were marketed in June 2005 and the ointment in July 2007, both as P medicines. The drug is routinely prescribed by primary care prescribers[11] for suspected cases of infective conjunctivitis and is the recommended first-line treatment.[12] Prior to OTC availability, community pharmacists were limited to selling antiseptic preparations such as propamidine and dibrompropamidine-

based products for ophthalmic infections.[13] The proposal to make ophthalmic chloramphenicol available OTC was welcomed by various groups of healthcare professionals and the public following widespread consultation. At the time the benefit of improved and timely access to treatment outweighed the risks associated with wider accessibility[14,15], although concerns regarding inappropriate over-supply, misdiagnosis by pharmacists and the emergence of increased bacterial resistance were raised.[16]

Recent findings

Since the launch of OTC ophthalmic chloramphenicol two main issues have come to light. First, pharmacy availability of ophthalmic chloramphenicol has been shown to have no impact on prescription supply for the same drug and, overall, there was a substantial increase in the supply of chloramphenicol in primary care in the first three years following reclassification.[17,18] Whether this situation remained the same beyond three years is unknown. Secondly, there is increasing clinical evidence that topical antibiotics are of limited benefit in infective conjunctivitis in primary care.[19] Given that the condition is, in most cases, self-limiting[20,21] and restricting use of antibiotics minimizes unnecessary treatment and emergence of resistance[22], the current consensus in managing these patients is to adopt the practice of 'no or delayed antibiotic' supply[23]. Recent evidence suggests this may have impacted on the prescribing of ophthalmic chloramphenicol by GPs[24] but whether supply OTC was affected remains unclear.

The aims of the study, therefore, were to (i) quantify the sales of OTC ophthalmic chloramphenicol from all community pharmacies in Wales and investigate the impact on primary care prescriptions up to five years after reclassification and (ii) investigate the temporal relationship between items supplied OTC and on NHS primary care prescriptions.

METHOD

The study had an ecological design and involved a retrospective analysis of prescription data and OTC sales data for ophthalmic chloramphenicol supplied in Wales.

Prescription data were extracted from CASPA.net (Comparative Analysis System for Prescribing Audit), an NHS Wales data store for primary care prescribing data. Data for all ophthalmic chloramphenicol preparations listed in the British National Formulary section 11.3.1[13], prescribed and dispensed in Wales were extracted from CASPA.net for the period June 2004 to December 2010 (12 months before and 66 months after OTC ophthalmic chloramphenicol availability).

OTC sales data were obtained from IMS Health and included four established proprietary brands of both chloramphenicol eye drops and ointment (Brochlor®, Golden Eye Antibiotic®, Galpharm Vision®, Optrex Infected Eyes®), together with one proprietary (Tubilux®) and one own-brand of eye drops. As at December 2010, there were two further proprietary brands of chloramphenicol eye drops available as P medicines in the UK [25] but data for these products were unavailable and thus not included in the analysis. Ophthalmic chloramphenicol preparations licensed as POMs, such as Minims eye drops, were excluded from the OTC sales analysis. The OTC sales data obtained were available from June 2005 to December 2010 (66 months) and represented the supply of ophthalmic chloramphenicol preparations from wholesalers into 614/708 (87%) NHS-contracted community pharmacies in Wales. Data for the remaining 94 NHS-contracted pharmacies and eight pharmacies without NHS contract were obtained direct from the pharmacy chain concerned (Company A) for the period January 2008 to December 2010 (36 months). OTC sales of chloramphenicol eye drops from Company A between June 2005 and December 2007 (30 months) and ointment between July

and December 2007 (6 months) were estimated using linear regression. The line of best fit generated from the model was extrapolated backwards based on available cumulative sales data. The OTC sales from Company A (estimated and actual) were combined with IMS Health sales data to give the total quantity of OTC ophthalmic chloramphenicol sold in Wales from June 2005 to December 2010.

Prescription and OTC supply

The total number of items supplied on prescription or sold OTC are presented as the 12-month totals for the eye drops, from June to May, and for the ointment, from July to June, to allow the comparison before and after their respective availability OTC. Correlation coefficient (r) for prescription items supplied and OTC sales of combined chloramphenicol eye drops and ointment was calculated using Spearman's rank correlation, based on actual prescribing and OTC sales data between January 2008 and December 2010.

All data analysis and statistics were performed using PASW version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

The linear regression model generated cumulative sales equations for eye drops (R^2=0.998, P<0.0001) and eye ointment (R^2=0.995, P<0.0001) for Company A and estimated cumulative sales for the respective periods when no data was available (data not shown). The total cumulative quantities of ophthalmic chloramphenicol sold OTC (IMS Health + Company A [actual and estimated OTC sales]) are shown in Figure 1.

The supply of chloramphenicol eye drops from 2004/05 to 2009/10 is shown in Figure 2. It

showed there was a steady increase in overall use of ophthalmic drops, prescribed and sold, from 2004/05 (86,916) to a peak in 2007/08 (142,013) before this plateaued in 2008/09 (134,220) and 2009/10 (133,942). The supply of OTC eye drops was at its peak in 2007/08, equivalent to 68% (57,708/84,305) of the respective number of items supplied on prescription. The largest year-on-year reduction in supply of prescription eye drops occurred in 2005/06 (-7%, 6,072/86,912), which corresponded to the period when OTC chloramphenicol eye drops were launched (June 2005). Subsequent changes were -3% (2,536/80,844), +7% (5,997/78,308), 0% (1/84,305) and 0.3% (282/84,306) from 2006/07 to 2009/10, respectively.

Ophthalmic chloramphenicol eye ointment was reclassified in 2007 and the subsequent quantities supplied are shown in Figure 3. The largest reduction of prescribed ointment compared with the previous year was seen in 2007/08 (-13%, 7,218/54,410) and coincided with the launch of OTC eye ointment in July 2007. During this period (2007/08), OTC sales of ointment were 48% (22,875/47,192) of their respective prescription volume. Subsequent sales of OTC ointment fell by 29% (6,563/22,875) in 2008/09 to 16,312 packs, equivalent to 31% (16,312/52,811) of the respective prescription volume and in 2009/10 OTC sales was 33% (17,061/51,410) of the respective prescription volume. The overall impact of OTC chloramphenicol ointment availability in 2007/08 was to increase its total supply in Wales by 29% (15,657/54,410) compared to the previous year, which then remained consistently higher than the quantities supplied in any other 12-month period before July 2007 when the ointment were only available on prescription.

A summary of the combined quantities of eye drops and ointment sold OTC or supplied on prescription is shown in Figure 4.

In the period January 2008 to December 2010, a marked seasonal variation for eye drops supplied on both prescription and sold OTC was observed, with peaks occurring between December to March and nadirs between August to October each year. In comparison, the supply of the ointment showed no discernable seasonal variation (Figure 5). Spearman's rank correlation revealed a significant and positive correlation between prescriptions and OTC sales of chloramphenicol eye drops and ointment combined ($r=0.7$, $p<0.001$).

DISCUSSION

The pharmacy sales data presented in this study are the first and the most comprehensive dataset studied to date and include data from all NHS-contracted community pharmacies in Wales. The results demonstrate that the availability of ophthalmic chloramphenicol OTC has contributed to an increase in the supply of chloramphenicol greater than previously identified.[18] Supplies of OTC chloramphenicol eye drops increased from 2005 to 2007 but have subsequently remained stable. Similarly, the availability of OTC eye ointment increased overall use in primary care. It would appear that despite the relatively large quantity of ophthalmic chloramphenicol being sold OTC, it has had little or no impact on prescription supply some five years after it was reclassified to a P medicine. As a consequence there has been no cost saving on drug expenditure for the NHS as was initially expected.[26] When the temporal relationship between OTC sales of ophthalmic chloramphenicol and items dispensed on prescription was explored, it was found that there was a positive relationship. This may, in part, suggest community pharmacists and primary care prescribers were responding to similar presenting symptoms but whether or not prescribing and/or OTC sales were appropriate is unclear.

Study Limitations

Primary care prescribing data was comprehensive, and extracted from an established and routinely used database that included details of NHS prescriptions dispensed by every community pharmacy in primary care in Wales. The OTC sales data were obtained from two sources: IMS Health and a pharmacy chain (Company A). Previous research noted that sales data collected by IMS Health only included 87% of all community pharmacies in Wales[18] and, as such, sales would underestimate the actual volume sold. In the present study, sales figures from Company A were obtained and complemented the IMS Health dataset. It should also be noted that two other branded products came to OTC market during the study. While data for these two products was not captured in the IMS Health dataset there appeared to be no impact on sales of the products monitored. Moreover we could identify the total amount of ophthalmic chloramphenicol prescribed and sold throughout the period of the study and this indicated sales of these new brands were negligible.

Unlike the IMS Health data, which were available for the entire post-reclassification period, sales data from Company A were only available from 2008 to 2010, and therefore the quantities sold during the first three years following OTC availability had to be estimated. It was possible that the sales pattern during the early months of a new product could have been markedly different. However, the available sales trend data from IMS Health for the other 614/708 community pharmacies in Wales indicated this was not an issue.

An important difference between the pharmacy sales data utilized in the present study is that while data from Company A represented transactions between pharmacy and customers, IMS Health data reported supplies from wholesalers to pharmacies. As with previous studies that have employed IMS Health sales data[18,24], the latter was identified to be a good proxy for pharmacy-to-customer sales. This relationship is likely to hold for chloramphenicol eye drops

as they need to be stored in a fridge, where space is usually at a premium, and bulk advance purchases unlikely. Advanced ordering in anticipation of increased demand associated with, for example, an upcoming advertising campaign, and/or bulk-purchase discount offers would have distorted sales figures but we have no evidence this was the case over the study period monitored.

The present study was limited by its ecological nature, and consequently we were unable to identify factors that caused the increased and sustained supply of ophthalmic chloramphenicol OTC. It was likely that the removal of barriers such as the need to make a GP appointment, improved access and cost of travelling to and from doctor's surgery provided sufficient incentive for people to practice self-care[3], even if individuals had to purchase the treatment themselves in a country with no co-payment prescription levy. Sales could have been stimulated by promotional activities and, as a result, improved the public's awareness of conjunctivitis and product availability. Although there was a temporal relationship between OTC sales and items supplied on prescription, suggesting that patients with similar presentations were turning up at both community pharmacies and GP surgeries and were supplied ophthalmic chloramphenicol. This result needs to be interpreted with caution as it only serves to demonstrate an association between the two variables rather than providing an explanation for them. To date there has been no published data that has evaluated the appropriateness of prescribing or OTC supply of ophthalmic chloramphenicol in primary care, even if such criteria could be defined.

Comparison with literature

Contrary to the trend of reduced prescribing for ophthalmic chloramphenicol reported in England[26], the number of prescribed items for both eye drops and ointment in Wales

remained similar despite the high volume of OTC sales following reclassification. This observation could have been influenced by the abolition of the NHS prescription charge in Wales (April 2007), which may have encouraged patients to obtain a free prescription from their doctor. In England where prescription co-payment was still in place, it was cheaper for patients who paid the prescription charge to purchase ophthalmic chloramphenicol OTC given the average price of eye drops and ointment were £4.72 and £5.24 respectively, whereas the cost of a prescription item was £6.50 in 2005 and £7.40 in 2011. Our data demonstrated that during the 12-month period (June 2007 to May 2008) after the abolition of prescription charge in Wales, there was a small but distinguishable increase in eye drops dispensed on prescription, which is consistent with the observation made by others of an increase in prescription items following abolition of the co-payment charge.[27] This was not observed with the ointment over the same period but is probably because the market had not matured or stabilized. It has been suggested that the decrease in the number of items prescribed for chloramphenicol eye drops and ointment in England was due to a change in the management of conjunctivitis from empirical prescribing to no or delayed prescribing.[24] Whether or not prescribers in Wales adopted this approach is unknown. Moreover, changes in prescriber preference, such as switching from one topical ophthalmic antibiotic to another may have confounded the picture.

Walker and Hinchliffe[17] reported a year-on-year increase in OTC sales of ophthalmic chloramphenicol eye drops in Wales during the three-year period post-reclassification. Likewise, Davis *et al*[24] reported a similar trend for England from 2005 to 2007. The present study demonstrates that sales of OTC chloramphenicol eye drops eventually stabilized four years post-reclassification. The seasonal variation observed for chloramphenicol eye drops sold OTC in Wales was consistent with the incidences of bacterial conjunctivitis reported by

Block *et al*[28], with peaks in the winter months of December to February and a low incidence in the summer months of June to August. It was noted that the ophthalmic ointment whether prescribed or sold OTC lacked the same seasonal feature. The reasons for this are unclear but probably related to the smaller quantity of ointment supplied and the preference of patients for the drops to avoid prolonged periods of blurred vision associated with the use of the ointment.

IMPLICATIONS

When ophthalmic chloramphenicol was reclassified in the UK, concerns were raised about the possibility of misdiagnosis[16] and the risk of bacterial resistance[29] due to inappropriate OTC supply. Over the five-year period following OTC availability, sales of ophthalmic chloramphenicol grew substantially before appearing to stabilize. Their apparent lack of impact on prescription use meant that there was no saving to the NHS drug budget nor a reduction to GP workloads. In view of the emerging evidence that support the practice of 'no or delayed antibiotic' in managing most primary care cases of acute conjunctivitis[21,22,29,31,32], the updated prescribing guidance for OTC ophthalmic chloramphenicol issued by the Royal Pharmaceutical Society was imperative and befitting.[33] Further monitoring is needed to determine whether pharmacists have subsequently embraced non-medicinal management such as eye bathing and postponing immediate antibiotic supply for acute bacterial conjunctivitis. It is recognised that the conventional signs and symptoms pharmacists' rely on to distinguish bacterial from viral conjunctivitis[33] are diagnostically non-informative.[34] It is not improbable that some of the increase in OTC ophthalmic chloramphenicol sales has arisen because of misdiagnosis and therefore reflects inappropriate use as some have recently suggested[35]. Further, it is not known from sales data to what extent, if any, medicines counter assistants (MCAs) have been involved in any of the OTC supplies. Further research on this

matter would be helpful as community pharmacists for many years have delegated some responsibility on OTC medicine sales to MCAs via medicines sales protocols[36], although more recently it has been reported that that MCAs do not always comply with guidelines when dealing with OTC consultations.[37]

CONCLUSION

Over the five-year study period, there was an increase in overall supply of ophthalmic chloramphenicol following availability from community pharmacies without prescription. The initial year-on-year increase in overall supply reported by others[17,24] appears to have stabilized four years post-reclassification while having little impact on prescription items over the entire study period. Despite a temporal relationship between OTC ophthalmic chloramphenicol supply and items dispensed on prescription, the appropriateness of supplies from community pharmacies remains unknown. The benefits and risks of having ophthalmic chloramphenicol available OTC and the impact of updated practice guidance on its prescribing OTC need to be studied further to better understand its current, high level of use.

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