SYSTEMIC ANTIBIOTICS FOR SELF MEDICATION: THE END OF THE LINE?

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ABSTRACT

The recent withdrawal in the United Kingdom (UK) of applications to reclassify two separate systemic antibiotics for uncomplicated cystitis in women as ‘P’ medicines (pharmacy only sale), marks the probable end of a 15 year discussion. The reasons for these withdrawals are not known, but they ended what had become a protracted regulatory process.

The potential for increased microbial resistance in the community following unsupervised use of antimicrobial agents raises important concerns. Illegal sales of systemic antibiotics in European pharmacies remain a substantial problem, and this ‘Over the Counter (OTC)’ antibiotic misuse, has sometimes prejudiced the debate about proposals for regulated self medication. The abandoned applications, for selected antibiotics in a restricted indication, argued that such de-regulation had the potential to improve antibiotic usage in these limited circumstances. This proposition will remain untested in the absence of prospective studies following an approval. However existing data on self medication of recurrent episodes of cystitis in women and known patterns of antibiotic use in this indication support the contention that not all self-medication with antibiotics would inevitably lead to misuse and worsening resistance.

The removal of two applications to re-classify systemic antibiotics has been seen as an important victory for the principle that systemic antibiotics should be restricted to prescription only use. This paper explores an alternative view that this move may represent a missed opportunity to encourage some responsible self care with antibiotics and to contrast that with the widespread misuse which currently prevails.

Key words: systemic antibiotics, OTC, pharmacy, ‘P’ medicine, bacterial resistance.

PROPOSALS FOR REGULATED SELF MEDICATION WITH SYSTEMIC ANTIBIOTICS - THE UK HISTORY

The recent withdrawal of applications for oral trimethoprim and nitrofurantoin to be available as ‘P’ medicines (sold under the supervision of a pharmacist) for the treatment of uncomplicated urinary tract infection in women, may be the closing chapter in a story which began almost 15 years ago. In 1996 the British Society for Antimicrobial Chemotherapy (BSAC) convened a working party in response to the increasing availability of antimicrobial agents for self medication from UK pharmacies. The previous year systemic fluconazole as a single dose treatment for vaginal candidiasis had been approved. The convenors judged that applications to ‘switch’ antibiotics to self medication status would follow, and sought to review the advantages and disadvantages of any such regulatory change.
The working party reported in 1999\(^1\), but the intervening years had seen a greatly increased public interest in the importance of increasing bacterial resistance to antibiotics, fuelled in part by political scrutiny of the issue\(^2\). The working party report was controversial in making a case for the licensing of a limited number of antibiotics, in clearly defined indications, as 'P' medicines.

The report also questioned widely held assumptions that any move to make antibiotics available for self medication would inevitably lead to greatly increased antibiotic usage. While this was likely to be the case for symptoms with poor links to a bacterial cause, such as sore throat, for which doctors would seldom prescribe, it was felt to be inherently unlikely in others e.g. in uncomplicated urinary tract infection (UTI) in women, where empirical treatment of symptoms with prescription antibiotics was common. The report also speculated that the availability of only selected antibiotics for self medication might even alter the pattern of antibacterial usage for the good, by substituting for some poor prescription choices. The working party concluded that only well characterised, well tolerated drugs with limited prescription indications and no or limited potential for cross-resistance to other antimicrobials could be considered suitable for self-medication. The list was further limited by consideration of which indications might be appropriate. Finally, only acute symptomatic uncomplicated UTI in adult women with a recurrence of typical symptoms following a previous doctor diagnosis was felt to be supportable for systemic antibiotic treatment, and even then only with an agent used solely for UTI\(^1\).

It was unsurprising that several companies made applications for systemic antibiotics to be made available for this latter indication, rehearsing all or part of the rationale detailed in the report.

New applications to reclassify medicines in the UK are evaluated by the Medicines and Healthcare product Regulatory Agency (MHRA) with advice from an expert committee (the Commission on Human Medicines). When these bodies judge that the proposed reclassification may be made safely, wide public consultation via the MHRA website takes place. Two applications proceeded to the public consultation stage: trimethoprim in 2005\(^3\) and nitrofurantoin in 2008\(^4\). Both restricted the indication for self medication to ‘uncomplicated acute bacterial cystitis in women aged between 16 and 70 years of age who have had the condition on a previous occasion when a physician confirmed the diagnosis.’ They also proposed additional label restrictions intended to minimise the potential for resistance to develop, including limiting the number of episodes self-treated within a year and early self-referral if symptoms persisted or relapsed rapidly.

Finally, in March of this year, it was announced that both applications had been withdrawn by the sponsors.

**PREDICTING THE IMPACT OF RE-CLASSIFICATIONS ON RESISTANCE**

The principal objection to allowing self medication with systemic antibiotics is that such usage would inevitably lead to misuse and/or overuse, primarily through mistaken diagnosis and
treatment of symptoms that do not have a bacterial cause. However, for the indication of recurrent episodes of uncomplicated cystitis in women, studies on self-diagnosis and patient-initiated treatment do not support this objection. Schaeffer and Stuppy evaluated self-treatment in 34 women with recurrent episodes of urinary tract infections (UTI). Women self-diagnosed and treated symptomatic episodes with an antibiotic, after obtaining a dip-slide culture, and were then re-supplied for the next episode. A total of 28 women suffered and treated 84 symptomatic episodes during 355 patient-months of follow up. The great majority (92%) of symptomatic episodes responded to the antibiotic and of 78 episodes when cultures were available, 11 were negative. A similar study of patient-initiated treatment in young women with uncomplicated recurrent urinary tract infection, documented 172 episodes of self-diagnosed infection in 88 women, with urine samples collected before self-medication. Laboratory evaluation showed absence of pyuria or bacteriuria in only 9 cases (5%), uropathogens in 144 cases (84%) and sterile pyuria in 19 cases (11%). The authors characterised 15 of these sterile pyuria episodes without an alternative diagnosis as ‘probable UTIs’. These data suggest that patient initiated treatment of symptoms suggestive of uncomplicated UTI is successful and that treatment of symptoms definitely not related to bacterial infection is uncommon.

If a systemic antibiotic were to become available for self-medication, it is generally assumed that usage of that antibiotic would grow substantially. In the case of recurrent uncomplicated UTI in women, it seems likely that any rise in usage would result from substitution of the self medication drug for prescriptions, rather than from treatment of more episodes. If the only drug available for self-treatment was urinary specific, e.g. nitrofurantoin, it is unlikely that such a shift in usage would affect resistance patterns amongst common uropathogens adversely. European Surveillance of Antimicrobial Consumption (ESAC), which collects antibiotic consumption data for public health purposes in all European countries, confirmed the usage of nitrofurantoin is respectively 9-fold and 4-fold greater in Belgium and the Netherlands (where nitrofurantoin is by far the most popular treatment for uncomplicated bacterial cystitis) than in the UK. Despite this heavy usage, data from the ECO•SENS project showed E.coli resistance to nitrofurantoin to be low in these countries (0.7% & 1%, respectively). Thus, empirically, even a large increase in usage of nitrofurantoin in the UK from the current low level, would be unlikely to impact important uropathogen resistance to the drug substantially. Conversely, a shift in usage away from non urinary specific antibiotics could reduce selection pressure for resistance to develop to those drugs.

The case for a non-urinary specific drug such as trimethoprim is not so clear. The argument that this drug is recommended for empirical use on prescription and therefore that self medication would simply substitute for some prescriptions is relatively weak, although the net impact on bacterial resistance would probably be modest.

The BSAC working party report reviewed the difficulties in obtaining sound epidemiological data on community resistance amongst pathogens and also commented on the possibility of conducting prospective surveys on the prevalence of resistance before and after the
introduction of an antibiotic for self medication. Such surveys would have posed considerable
difficulties, but an agreed study could have been made a condition of any approval.

UNREGULATED SELF MEDICATION WITH SYSTEMIC ANTIBIOTICS

In 2001, the Council of the European Union (which determines general political guidelines for
the EU) issued a recommendation to Member States that they should ‘implement control and
preventative measures to support the prudent use of antimicrobial agents and contribute to
limiting the spread of communicable diseases by: a) restricting systemic antibacterial agents to
prescription-only use’.

Subsequent work in follow up to this recommendation has illustrated
that use of systemic antibiotics without prescription is currently widespread in Europe, despite
the fact that such usage is not legal in any member state.

The SAR-project (Self Medication with Antibiotics and Resistance), reported in summary in a
paper on member states implementation of the Council recommendation, and subsequently
published in full, surveyed the use of systemic antibiotics without prescription in European
countries. In 2003 a mailed questionnaire was sent to a total sample of 39,754 adults in 19
countries of whom 15,548 (39%) responded. The analysis was limited to systemic antibiotics,
i.e. drugs that should not have been available over the counter (OTC) in any of the countries.
The survey reported actual and ‘at risk’ (intended use and storage at home) self medication
with antibiotics.

Figure 1: Actual self medication with systemic antibiotics and categories ‘at risk’ for use of self
medication in 19 countries of Europe (reported rates in previous 12 months per 1000
population). Published in reference 9.
Figure 1 shows self medication split into these ‘categories’ of actual or intended use, and reveals marked differences between countries, but with broadly similar behaviour patterns within the North, South, East and West regions of Europe.

The source of these illegitimate supplies is summarised in Table 1 taken from the same report. Direct supply from the pharmacy without a prescription and ‘leftovers’ from prescriptions were the most important sources of actual self medication reported in the previous 12 months. In some countries in the South (Spain and Malta) and the East (Romania, Lithuania, Czech Republic), more than 50% of the self medication courses came directly from the pharmacy.

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<thead>
<tr>
<th>Table 1: Source of supply for episodes of self-medication in figure 1 (adapted from reference 9)</th>
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<tr>
<td><strong>percentage of courses, all countries</strong></td>
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<tr>
<td>Purchased in pharmacy - own country</td>
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<tr>
<td>Purchased in pharmacy - abroad</td>
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<tr>
<td>Leftover from prescription</td>
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<td>Friend or relative</td>
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* 38 courses had more than one source

The misuse of prescription antibiotics by consumers and the attitudes which lead to this have been well described in the US\textsuperscript{11}. The instinct to hoard prescription drugs for future self medication is clearly an aspect of consumer behaviour to which considerable educational effort needs to be directed.

The proposals for limited self medication in particular indications and with specific antibiotics in the UK are relevant to this existing cultural and educational problem. The contrast between limited, regulated self medication and the opportunism that operates now would have been striking, and may have helped consumers to make the right choices. In this regard, the UK experience could have served as a valuable test of the true impact of regulated change in antibiotic availability.

**THE FUTURE – MORE EDUCATION AND REGULATION NOT MORE AVAILABILITY?**

Recent calls for better antibiotic stewardship have equated any possible extension of availability for systemic antibiotics with an inexorable rise antibiotic resistance. This linkage is based, in part, on an untested assumption: that self care availability means ‘inevitably wider sales’\textsuperscript{12}. However, with restricted indications, such as repeat episodes of cystitis, the evidence does not suggest that more episodes would be self-treated than on prescription and it is difficult to see
how antibiotic use would grow substantially.

Another frequently voiced concern is that the issuing of a prescription provides the only way to connect surveillance of antibiotic use to surveillance of resistance\textsuperscript{12}. However sales of specific non-prescription medicines are tracked by sophisticated systems for commercial purposes, and could provide at least as comprehensive a picture of regional usage as prescription data, if that was to be requested by regulators. Also surveillance of resistance patterns amongst pathogens is dependent on clinical practice. For example, current guidelines in the UK\textsuperscript{13} recommend empirical prescription of antibiotics for typical symptoms of cystitis in women, without taking a sample of urine for culture. Thus the current arrangements for surveillance in this condition would have been unchanged by self medication.

CONCLUSION

It seems unlikely that wider self medication with systemic antibiotics, even in very carefully limited circumstances, will now happen in the UK. The proposition that particular proposals could have produced benefit, rather than harm, to community bacterial resistance will probably remain untested.

A blanket ban on systemic antibiotics for self medication in Europe and elsewhere has the virtue of simplicity, but does not differentiate between proposals for regulated use and the widespread unregulated supply which now exists. While consumers perceive an unmet need for treatment of their infections, we can expect misuse of antibiotics that they hoard from previous prescriptions to continue. The very existence of a carefully regulated supply for self medication might have provided valuable opportunities to educate consumers in the importance of correct antibiotic usage.

Antibiotic stewardship is an important responsibility for society, but correct antibiotic usage is ultimately in the hands of the consumer. The balance between the benefits of self care and the potential for societal harm is different for systemic antibiotics than for other drugs. However this should not mean that we replace a careful case-by-case evaluation of risks and benefits with a blanket policy that has the effect of equating possible future regulated self medication with the current unregulated misuse of systemic antibiotics.

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Disclosure: The author has acted as a consultant to several pharmaceutical companies on issues related to self medication with antibiotics.
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