Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis

Martin H. Thornhill1,2*, Mark J. Dayer3, Bernard Prendergast4, Larry M. Baddour5, Simon Jones6 and Peter B. Lockhart2

1Unit of Oral and Maxillofacial Surgery and Medicine, University of Sheffield School of Clinical Dentistry, Claremont Crescent, Sheffield S10 2TA, UK; 2Department of Oral Medicine, Carolinas Medical Center, Charlotte, NC 28203, USA; 3Department of Cardiology, Taunton and Somerset NHS Trust, Taunton, Somerset TA1 5DA, UK; 4Department of Cardiology, John Radcliffe Hospital, Oxford OX3 9DU, UK; 5Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, MN 55905, USA; 6School of Health Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK

*Corresponding author. Tel: +44-(0)114-271-7857; Fax: +44-(0)114-271-7863; E-mail: m.thornhill@sheffield.ac.uk

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Objectives: Antibiotic prophylaxis (AP) administration prior to invasive dental procedures has been a leading focus of infective endocarditis prevention. However, there have been long-standing concerns about the risk of adverse drug reactions as a result of this practice. The objective of this study was to identify the incidence and nature of adverse reactions to amoxicillin and clindamycin prophylaxis to prevent infective endocarditis.

Methods: We obtained AP prescribing data for England from January 2004 to March 2014 from the NHS Business Services Authority, and adverse drug reaction data from the Medicines and Healthcare Products Regulatory Agency’s Yellow Card reporting scheme for prescriptions of the standard AP protocol of a single 3 g oral dose of amoxicillin or a single 600 mg oral dose of clindamycin for those allergic to penicillin.

Results: The reported adverse drug reaction rate for amoxicillin AP was 0 fatal reactions/million prescriptions (in fact 0 fatal reactions for nearly 3 million prescriptions) and 22.62 non-fatal reactions/million prescriptions. For clindamycin, it was 13 fatal and 149 non-fatal reactions/million prescriptions. Most clindamycin adverse drug reactions were Clostridium difficile infections.

Conclusions: AP adverse drug reaction reporting rates in England were low, particularly for amoxicillin, and lower than previous estimates. This suggests that amoxicillin AP is comparatively safe for patients without a history of amoxicillin allergy. The use of clindamycin AP was, however, associated with significant rates of fatal and non-fatal adverse drug reactions associated with C. difficile infections. These were higher than expected and similar to those for other doses, durations and routes of clindamycin administration.

Keywords: adverse drug reactions, amoxicillin, clindamycin, dental

Introduction

Infective endocarditis (IE) is an infection of the endocardium that is associated with high morbidity and mortality.1 Bacteria from the oral cavity, particularly oral viridans group streptococci, are implicated as the causal organisms in ≈35%–45% of cases.2–6 Consequently, dentists have historically given antibiotic prophylaxis (AP) to patients at risk of developing IE prior to performing invasive dental procedures.

The aim of AP is to reduce or eliminate bacteraemia caused by procedures7–11 that may lead to IE in susceptible individuals. However, there has never been a randomized clinical trial to demonstrate the effectiveness of AP12 and there is little evidence to support its effectiveness.3,5,9 Furthermore, concerns have been expressed that the cost and potential adverse effects of AP may outweigh its benefits.13–16

Until recently, it was the standard of care in most parts of the world to provide AP to patients at high risk (previous IE, prosthetic heart valves or valves repaired with prosthetic material, unrepaired cyanotic congenital heart disease or certain repaired congenital heart defects) or moderate risk (previous rheumatic fever, heart murmur or evidence of native valve disease) of IE.

However, in March 2008 the UK National Institute for Health and Care Excellence (NICE) produced guidance recommending cessation of AP for preventing IE.17 In contrast, the American Heart Association (AHA)18 and the European Society for Cardiology (ESC)19 produced guidelines in 2007 and 2009, respectively, that recommended cessation of AP only for individuals at moderate risk of IE.
The move to reduce AP prescribing was driven not just by lack of evidence for efficacy, but also by concerns about the risk of adverse drug reactions (ADRs), the risk of increasing antibiotic resistance and cost. The aim of this study was to quantify the risk and nature of adverse events associated with AP in England.

**Methods**

Prior to introduction of the NICE guidelines, a single 3 g oral dose of amoxicillin (or a 600 mg oral dose of clindamycin in penicillin-allergic individuals, or those who had received amoxicillin during the previous month) was prescribed before invasive dental procedures as AP to those at moderate or high risk of developing IE. This dosage schedule and route of administration for amoxicillin and clindamycin are almost exclusively used for AP purposes.\(^{20,21}\) Data on their prescribing between January 2004 and January 2014 were obtained from the National Health Service Business Services Authority (http://www.nhsbsa.nhs.uk/prescriptions). We have previously published data on AP prescribing for earlier periods.\(^{20,21}\)

The Medicines and Healthcare Products Regulatory Agency (MHRA) provide ADR data using the Yellow Card reporting scheme (http://www.mhra.gov.uk/SafetyInformation/MedicinesInformation/index.htm). ADR data were available for any dose, duration or route of administration of amoxicillin for the period from 1 July 1963 to 29 August 2014, and for clindamycin from 1 July 1963 to 20 August 2014. For a single 3 g oral dose of amoxicillin, however, it was only possible to extract data for the period from 13 January 1980 to 15 January 2014, and for a single 600 mg oral dose of clindamycin from 18 December 1969 to 15 January 2014. To estimate the ADR incidence for a single 3 g oral dose of amoxicillin or a single 600 mg oral dose of clindamycin, monthly prescribing data for the period January 2004 to March 2013 were used. For earlier periods, the mean number of prescriptions per month during the period January 2004 to March 2008 was used to extrapolate the data.

Unless specifically stated otherwise, the data presented are for England only.

**Results**

**Prescribing of amoxicillin AP**

Monthly prescribing data for all prescriptions of a single 3 g oral dose of amoxicillin are shown in Figure 1(a) with breakdown according to prescriber status in Figure 1(b).

Before the introduction of the NICE guidelines, 93.4% of all prescriptions for a single 3 g oral dose of amoxicillin were written by dentists and 6.6% were written by general practitioners. Prescribing by hospitals (0.2%) and nurses (<0.1%) was infrequent.

Following introduction of the NICE guidelines, there was a dramatic (87.8%) fall in the prescribing of amoxicillin AP, from a mean of 8395 prescriptions per month before NICE to a mean of 1026 prescriptions per month in the 6 months from July 2013 to January 2014 (P<0.001). Following the NICE guidelines, there was a small reduction in the proportion of prescriptions written by dentists (from 93.4% to 89.3%) and a compensatory rise in the proportion written by general practitioners (from 6.3% to 10.2%).

**Prescribing of clindamycin AP**

Data are shown for prescriptions for a single 600 mg dose of oral clindamycin (Figure 1a and c). Before the introduction of the NICE guidelines, 88.8% of all prescriptions for clindamycin AP were written by dentists and 10.9% by general practitioners. Prescribing by hospitals (0.2%) and nurses (<0.1%) was infrequent. Following introduction of the NICE guidelines, there was a marked decline (95.2%) in prescribing of clindamycin AP, from a mean of 2504 prescriptions per month before NICE to a mean of 120 prescriptions per month in the 6 months from July 2013 to January 2014 (P<0.001). Following the NICE guidelines, there was a substantial reduction in the proportion of prescriptions written by dentists (from 88.8% to 66.6%) and a compensatory rise in the proportion written by general practitioners (from 10.9% to 32.5%).

Taken together, there was an 89.5% reduction in the number of courses of AP prescribed (amoxicillin or clindamycin) following introduction of the NICE guidelines, from a mean of 10900 per month in the period January 2004 to March 2008 to a mean of 1146 in the last 6 months of the study (P<0.001) (Figure 1a).

**Incidence of amoxicillin-related adverse events**

Analysis of ADR reports for all doses, durations and routes of administration of amoxicillin (as a single active constituent) during the period July 1963 to August 2014 revealed 73 fatal reports, 5 of which were recorded as immune system and 13 as allergy-related skin disorders. There were also 3072 non-fatal reports, including 304 immune system and 2063 allergy-related skin reports. Analysis of amoxicillin prescribing data for all purposes between 2004 and 2007 demonstrated an average of 12896.805 courses per annum. Assuming a constant prescribing rate over the 51 years of data availability, this allows a crude estimate of 0.11 fatal and 4.67 non-fatal reactions per million courses of amoxicillin prescribed. Since amoxicillin prescribing has gradually increased over the period of ADR reporting, this probably represents an underestimate of the current frequency of reported adverse events for amoxicillin.

In contrast, analysis of ADR reports (where relevant data were available concerning dose and route of administration) revealed no fatal reaction reports following a single 3 g oral dose of amoxicillin during the data-recording period from January 1980 to January 2014. There were, however, 67 non-fatal reaction reports in the same period, 16 of which were recorded as immune system disorders (anaphylactic/allergic reactions) and 38 as allergy-related skin disorders (rashes, angioedema, pruritis and urticaria). Over the same period, we estimate that 2961.900 courses of a single 3 g oral dose of amoxicillin were prescribed. Using these figures, a crude estimate of the adverse reaction reporting rate was 0 fatal and 22.62 non-fatal reports per million courses of prescribed amoxicillin AP (of which 18 could be allergy related). For the period before introduction of the NICE guidelines, this equates to 0 fatal and 2.28 non-fatal (but reportable) reactions per annum. For the level of AP prescribing during the most recent 6 months of the post-NICE guidelines period, this equates to 0 fatal and 0.28 non-fatal reports per annum.

**Incidence of clindamycin-related adverse events**

The association of clindamycin with C. difficile infection is well documented and accounted for 41 (77.4%) of 53 fatalities reported for clindamycin between July 1963 and August 2014 (32 reported as C. difficile infections and 9 as gastrointestinal disorders). There was one immune-related skin fatality and one allergy-related skin fatality. The majority of fatalities were related to C. difficile infection. During the same period, 1273 non-fatal
Figure 1. Amoxicillin and clindamycin AP prescribing data. (a) Number of AP prescriptions dispensed each month (red, single 3 g oral dose of amoxicillin; blue, single 600 mg oral dose of clindamycin). Figure 1(a) is similar to a figure we recently had published in Lancet, but shows a further 10 months of data.21 (b) Number of amoxicillin AP prescriptions dispensed each month, by prescriber (red, dentists; blue, general practitioners; green, hospitals; purple, nurses). The numbers of hospital and nurse prescriptions are too small to see easily. (c) Number of clindamycin AP prescriptions dispensed each month, by prescriber (red, dentists; blue, general practitioners; green, hospitals; purple, nurses). The numbers of hospital and nurse prescriptions are too small to see easily. In each case, the grey bars indicate March 2008, when NICE recommended the cessation of AP for IE. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.
Adverse reactions to endocarditis prophylaxis

Adverse reactions to amoxicillin

The risk of fatal anaphylaxis with penicillin has previously been estimated at 1:100000 and is higher in those receiving parenteral rather than oral penicillin.22 Clemens and Ransohoff23 estimated the death rate associated with oral penicillin to be closer to 0.9 deaths per million courses and the severe and mild ADR rates to be 400 and 4480 per million courses, respectively. However, the risk associated with amoxicillin is less well documented. In a cost-deaths per million courses and the severe and mild ADR rates to the death rate associated with oral penicillin to be closer to 0.9

fatal (0.9/million) or severe (400/million) reactions calculated by Clemens and Ransohoff.23 Looking specifically at the risk associated with a single 3 g oral dose of amoxicillin, as used for AP in the UK, no fatal ADRs were reported over a period encompassing nearly 3 million prescriptions. This suggests that the incidence of fatal ADRs associated with a single 3 g oral dose of amoxicillin is considerably less than previously estimated for AP-related ADRs, or that for other doses/routes of amoxicillin administration. However, at 22.62 per million prescriptions, the rate of non-fatal ADRs associated with amoxicillin AP in the UK, while considerably less than previous estimates,23 appears similar to that for all other doses and routes of administration of amoxicillin in the UK.

Adverse reactions to clindamycin

Although the association of clindamycin with C. difficile infection is well established,24 estimates of its frequency range from 0.01% to 10%.26−29 In contrast, the occurrence of other ADRs to clindamycin, such as anaphylaxis, is thought to be rare.30,31 Our data suggest a rate of 11 fatal and 270 non-fatal reactions of all types per million courses of clindamycin. This is lower than previous reports in the literature, although our study examines the community-wide use of clindamycin, whereas previous studies were largely performed in hospital settings and among patients more susceptible to C. difficile infection.

With regard to the use of a single 600 mg oral dose of clindamycin for AP, there are no reliable data that address the incidence of ADRs. It had been thought that use of a single dose of clindamycin for AP purposes would not predispose to C. difficile infection.32 However, there have been five case reports following dental use of clindamycin,33 including one specifically related to the use of clindamycin for AP.34 For an assessment of the cost-effectiveness of AP in preventing IE, Agha et al.14 estimated a fatal ADR rate of 0/million and a non-fatal ADR rate of 4000/million for clindamycin. In our study, we estimated a rate of 13 fatal and 149 non-fatal reported ADRs per million courses of clindamycin AP, the majority related to C. difficile infection. Clearly, this is a much higher fatal ADR rate than previously estimated and similar to our rates for all other uses of clindamycin (11/million). While the non-fatal ADR rate was considerably less than previously estimated (4000/million),14 it was again similar to our rates for all other uses of clindamycin (270/million). These data suggest that use of clindamycin for AP carries a significant risk of ADRs that is very similar to the risk associated with the use of clindamycin for treating infections. In the literature, risk factors for developing C. difficile infections, aside from antibiotic use, include age and the use of proton pump inhibitors.35,36 Increasing age, malignancy, chronic renal failure and increased co-morbidity are thought to be risk factors for a poor outcome.37 Our study also provides human confirmatory data to support a recent mouse study that identified profound changes in intestinal microbiota leading to C. difficile infection following a single dose of clindamycin.38

Assuming that the change in AP prescribing that occurred following introduction of the NICE guidelines did not alter the rate at which ADRs occurred, it is possible to calculate the likely impact of the NICE guidelines on the number of ADRs occurring each year as a result of AP prescribing. With a mean of 8395 prescriptions for amoxicillin AP per month before NICE and 1026 after, the mean annual reported ADR rate would have been 0 fatal and 0.19 non-fatal reactions before NICE and 0 fatal and 0.02 non-fatal reactions after—in both cases very low. For clindamycin AP, with
2504 prescriptions per month before NICE and 120 after, the mean annual reported ADR rate would have been 0.03 fatal and 0.37 non-fatal reactions before NICE and <0.002 fatal and 0.02 non-fatal reactions after.

This raises a question over the suitability of clindamycin as an alternative for AP in those who report allergy to penicillins, particularly in those countries where AP is still the recommended standard of care. Recent studies have indicated that rates of cross-reaction between penicillins and first- and second-generation cephalosporins are much lower than previously thought and that cephalosporins are associated with low rates of serious ADRs compared with clindamycin.39–42 Perhaps it is time to re-evaluate whether cephalosporins, or other antibiotics, would be a safer alternative to clindamycin for AP purposes in those with a history of allergy to penicillins.

**AP prescribing**

Before introduction of the NICE guidelines in March 2008, there were an average of 8395 prescriptions per month for a single 3 g oral dose of amoxicillin and 2504 per month for a single 600 mg oral dose of clindamycin. The vast majority were issued by dentists, a small proportion by general practitioners and a tiny fraction by hospitals and nurses. Approximately 23% of patients requiring AP therefore had clindamycin. The reasons for this are likely a combination of self-reported allergy, and because the older guidelines in place in the UK, prior to the NICE guidelines, suggested that if a patient had had amoxicillin in the previous month then they should receive clindamycin as AP. Although we are not aware of any other studies of self-reported penicillin/amoxicillin hypersensitivity rates in the primary care dental setting, the rate reported in the primary care medical setting is approximately half this figure.41–45 The true rate of penicillin allergy is likely to be much lower, however. Around 2%–5% of patients reporting a penicillin ‘allergy’ are found to be allergic when formally tested, and the remainder will tolerate penicillin use.46–48 This has raised concerns that many patients labelled penicillin allergic, but who are in fact not allergic, are denied penicillins in favour of antibiotics with potentially worse side effects, such as clindamycin, vancomycin or quinolones.41 Better screening of patients with self-reported penicillin allergy, through better questioning and/or formal allergy testing, could significantly reduce the number of individuals denied penicillins.39,41,43,46–48

Following introduction of the NICE guidelines, there was a highly significant fall in the prescribing of both AP preparations (87.8% for amoxicillin, 95.2% for clindamycin). This fall affected prescribing by dentists and general practitioners but was proportionately higher amongst dentists. With the fall in AP prescribing, the proportion of patients receiving clindamycin also fell from a fairly steady ~23% before the NICE guidelines to just 10% in the last 6 months studied. This fall may reflect the fact that after the NICE guidelines, for patients with a self-reported penicillin allergy, the practitioner was more likely to elect to give no AP than to give clindamycin as an alternative to amoxicillin.

Although AP is no longer recommended before invasive dental procedures for any patients in the UK, it is still the standard of care for patients at high risk of IE in most parts of the world.16,19 In the USA and some other parts of the world, AP using oral amoxicillin or clindamycin is often also prescribed before invasive dental procedures for patients with prosthetic joints and a range of other conditions.16 Indeed, Lockhart et al.16 have calculated that between 4.9 and 35.6 million courses of AP may be prescribed before invasive dental procedures annually in the USA at a cost of between $19.9 and $143.7 million.

**Limitations**

In the UK, the Yellow Card reporting scheme is used by clinicians, including dentists, to report adverse drug reactions to the MHRA. Reporting by healthcare professionals is voluntary and not all adverse reactions are reported. Reported reactions may omit important data or be confounded by other factors. It is also not always certain that the drug identified caused the reported reaction—instead this could relate to the disease being treated, other drugs or completely unrelated factors. Moreover, it is known that healthcare workers are more likely to report serious or fatal ADRs than non-serious reactions. Furthermore, reporting is more common for newer drugs or those with a high public profile than for older established drugs such as amoxicillin and clindamycin. It is also likely that there are minor adverse events that patients fail to report. It is likely, therefore, that these data underestimate the incidence of adverse reactions. These limitations, however, are shared by most other voluntary ADR reporting schemes that have been used to estimate ADR rates.

A further limitation is that we did not have access to the indication for the antibiotic being prescribed. However, there are few, if any, indications for a single 3 g oral dose of amoxicillin or a single 600 mg dose of clindamycin other than to prevent IE. The dramatic fall after the change in NICE guidance suggests that this was the principal indication. Furthermore, ~92% of prescriptions were issued by dentists. We cannot exclude the possibility that some were prescribed for other reasons, however. Anecdotally, in recent years some dentists have started to use this dose prior to dental implants or to treat a dental infection. This may account for some of the residual prescribing.

**Conclusions**

APADR rates in England are low, and lower than previous estimates, with no fatal ADR recorded for nearly 3 million prescriptions of 3 g of amoxicillin as a single oral dose and 22.62 non-fatal ADR reported per million prescriptions. Use of amoxicillin AP for patients without a previous history of amoxicillin allergy appears safe. In contrast, the use of clindamycin AP was associated with a sizable ADR rate, including 13 fatal and 149 non-fatal ADR reports per million prescriptions, the majority relating to *C. difficile* infection. These findings should be incorporated into future discussions concerning the role of AP in the prevention of IE and calculations concerning its clinical and cost-effectiveness.

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Transparency declarations
M. J. D. is a topic expert (non-voting) for the current NICE review of clinical guideline 64. B. P. was a member of the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC) that produced the 2009 ESC guidelines on the Prevention, Diagnosis and Treatment of Infective Endocarditis. B. P. also acted as a consultant to the committee that produced the NICE clinical guideline 64 on Prophylaxis Against Infective Endocarditis. L. M. B. and P. B. L. are members of the American Heart Association’s Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease and were involved in producing the 2007 American Heart Association guideline on Prevention of Infective Endocarditis. M. H. T. and S. J.: none to declare.

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