Results of a UK survey of fatal anaphylaxis after oral amoxicillin

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Sir,

A single high dose of oral amoxicillin has been the main antibiotic regimen recommended for the prophylaxis of endocarditis since 1982, and there has been good compliance with this recommendation in the UK. However, the fear that the number of deaths from anaphylaxis associated with amoxicillin prophylaxis could exceed the number of deaths from endocarditis that might be prevented from prophylaxis was one factor leading the BSAC Working Party to discontinue recommending prophylaxis for most susceptible cardiac patients undergoing dental procedures.

We would like to contribute information from data which should be taken into account in discussions around the risk/benefit considerations. This may be particularly appropriate now as The Department of Health has asked the National Institute for Health and Clinical Excellence (NICE) to prepare guidance on antimicrobial prophylaxis for endocarditis in patients undergoing interventional procedures and to review the risks and benefits of antibiotics.

The MHRA collects information on suspected adverse drug reactions (ADRs) via the Yellow Card Scheme. The scheme was set up in 1964 and receives reports of suspected ADRs directly from healthcare professionals and more recently from patients. Healthcare professionals are requested to report ADRs to the Yellow Card Scheme, even if there is only a suspicion that a medicine may have caused the reaction, by using the yellow pages in the British National Formulary or online at http://www.mhra.gov.uk/home/idcplg?idcService=SS_GET_PAGE&nodeId=287. It is a statutory requirement that pharmaceutical companies report suspected ADRs to the scheme.

The MHRA’s database contains a total of 4333 UK reports of spontaneous suspected ADRs in association with amoxicillin between 13 February 1972 and 2 May 2007. There are a total of eight fatal cases of anaphylaxis; of which, five had an intravenous route of administration and in two cases, the route was unknown. There was only one case of fatal anaphylaxis in association with oral amoxicillin; this was in a female patient prescribed 250 mg orally four times daily for an unknown indication. The MHRA are not aware of any fatal cases reported with the single 3 g oral dose of amoxicillin that is recommended for prophylaxis of endocarditis in adults and none with any oral dose of amoxicillin in children. However, it is important to note that information on suspect drug dose and indication may not always be provided by the original reporter; therefore, the data must be interpreted with caution. We are not aware of any published literature case reports from the UK of fatal anaphylaxis, following oral amoxicillin prophylaxis of endocarditis.

The risk of fatal anaphylaxis with penicillin has previously been estimated as about 1 in 100 000 and is greater in those receiving penicillin parenterally than orally. However, the risk with other β-lactam antibiotics, including amoxicillin, is poorly documented. In recent correspondence relating to the latest BSAC guidelines to prevent endocarditis, it was suggested that there was a fatal anaphylaxis rate of 20 per million, although this was in association with ampicillin as well as amoxicillin and did not differentiate between parenteral and oral administration of these antibiotics. Yellow Card data cannot be used to determine the incidence of a particular ADR as denominator data are not available, and causality is not certain. Reporting by health professionals is entirely voluntary, and not all ADRs are reported, while those received may omit relevant data, or may be confounded by other factors. Although healthcare professionals are more likely to report serious or fatal suspected ADRs than non-serious reactions, it is a fact that the reporting of ADRs for many older drugs such as amoxicillin is much lower than that for newer drugs. In addition, reporting of some ADRs may reflect elevated public profile rather than true incidence.

The American Heart Association committee report about preventing endocarditis also noted that it was unaware of any reports of fatal anaphylaxis associated with the antibiotic prophylaxis of endocarditis in the USA during the last 50 years, and oral amoxicillin has also been the mainstay of the recommended regimens during the last 20 years.

Within the aforementioned limitations of spontaneous reporting for estimating the frequency of serious adverse reactions, the reporting rate from data available in the Yellow Card Scheme for oral amoxicillin is extremely low given the recently quoted risk of death from anaphylaxis in recent correspondence relating to the latest BSAC guidelines. Although it is not possible to easily obtain usage data for oral amoxicillin for the last 35 years, usage data for the last 5 years suggest that there were approximately 100 million treatment courses of oral amoxicillin during this time period. Although it is not possible to infer an incidence rate from the reporting rate, the receipt of only a single fatal case report of anaphylaxis definitively associated with oral amoxicillin in 35 years is worthy of consideration with respect to the vast experience in the use of this antibiotic.

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Sir,

We recently published a paper describing the distribution of OXA and IMP β-lactamasies in Acinetobacter spp. from Singapore.1 Since that manuscript was submitted, there has been accumulating evidence suggesting that OXA-51-type β-lactamasies are ubiquitous in Acinetobacter baumannii sensu stricto.2

To resolve the identity of isolates from our original study that were identified using biochemical tests as A. baumannii, but were negative for blaOXA-51-type genes, we used PCR to re-test all 12 strains using a new set of universal blaOXA-51-type primers.3 We also sequenced the 16S rDNA gene (first 500 bp) using primer 8FPL described by Relman4 and in-house primer 515R (S'-TTA CCG CGG CAG CTG GCA C-3'), and the 16–23S rRNA gene intergenic spacer using the primers described by Chang et al.5 In addition, we tested for the presence of the efflux genes adeB, adeE and adeY using the primers described by Chu et al.6 since it has been shown that the AdeABC multidrug efflux pumps are intrinsic to A. baumannii, whereas the AdeDE and AdeXY pumps are found predominantly in Acinetobacter genomospecies 3.

The final definition of strains to species level was based primarily on the 16–23S rRNA gene intergenic spacer sequences but also took into consideration the results of all the other tests (Table 1). Five strains were positive for blaOXA-51-type genes with the new primer set and remain identified as A. baumannii. Another five strains were re-identified as either Acinetobacter genomospecies 3 or Acinetobacter genomospecies 13TU. Conflicting results did not allow us to discriminate within the Acinetobacter calcoaceticus–Acinetobacter baumannii complex for two isolates.

The segregation of carbapenemase genes between the different Acinetobacter genomospecies is striking (Table 1). Of particular note, the IMP-4 metallo-β-lactamase is found in either Acinetobacter genomospecies 3 or Acinetobacter genomospecies 13TU but not in A. baumannii. Our data do support the hypothesis that blaOXA-51-type genes are intrinsic to A. baumannii. The distribution of efflux genes is also consistent with that reported by Chu et al.6

The A. calcoaceticus–A. baumannii complex is composed of four closely related species (A. calcoaceticus, A. baumannii, Acinetobacter genomospecies 3 and Acinetobacter genomospecies 13TU), which are difficult to differentiate phenotypically using traditional laboratory biochemical tests and commercial kits. In routine clinical practice, this distinction between the species is not usually clinically relevant and is rarely attempted. However, it may be important to define members of the A. calcoaceticus–A. baumannii complex to species level when describing the presence of β-lactamasies and other resistance determinants. As Turton et al.2 suggest, β-lactamase-genespecific PCR may be a good way to speciate Acinetobacter spp.

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Carbapenemase and efflux pump genes in Acinetobacter calcoaceticus–Acinetobacter baumannii complex strains from Singapore

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