with these data, microbiologists, clinicians and regulatory authorities might be better able to develop strategies that ensure a more rational use of antimicrobials, thereby prolonging their efficacy.

References


On achieving consensus on the prevention of malaria

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The giving of drugs to healthy people to prevent a disease of low probability demands an almost impossible level of safety from the compound used. Chloroquine’s 50 year safety record must be unique amongst antimicrobials and it is only the emergence of drug resistance which has forced prescribers to look elsewhere. Not surprisingly, some promising alternative contenders have failed to measure up: sulphadoxine/pyrimethamine (Fansidar) and amodiaquine were both summarily abandoned as prophylactics after they were implicated in clear-cut serious adverse advents. The latest compound to be officially endorsed as a chemoprophylactic, mefloquine (Lariam), has come under intense pressure from the media in the UK for over a year because of adverse effects that are often subjective and far from clear-cut.

In considering the risk/benefit ratio for mefloquine it is clear that, at present, it provides the best protection against Plasmodium falciparum malaria in visitors to sub-Saharan Africa. Observations on American Peace Corps volunteers in West Africa from 1989 to 1992 demonstrated that weekly mefloquine was 86% more effective than prophylaxis with chloroquine plus proguanil.1 When breakthrough infections in over 145,000 Swiss travellers who had stayed in East Africa for less than 1 year were analysed it was found that in people who used no chemoprophylaxis the incidence of P. falciparum malaria was 1.2% per month; mefloquine gave 91% protection, compared with 72% for chloroquine and proguanil.2 More recently a three-fold reduction in P. falciparum malaria imported into the UK from Kenya against a background of apparently stable malaria transmission led to the conclusion that the best explanation appeared to be the widespread use of mefloquine and a reduction in the use of chloroquine and proguanil by travellers.3 The only dissenting data came from The Netherlands with the report of P. falciparum infections in several travellers who had been taking mefloquine during October and November 1994.4 The authors proposed that, when the compound was started only 1 week before departure for a malarious area, protection might be sub-optimal for those infected early in the course of their visit since steady-state serum concentrations of mefloquine are reached only after 6–8 weeks.4

Adverse effects of drugs taken to prevent malaria are remarkably common.3,6 A postal and telephone survey conducted among British travellers between November 1993 and February 1995 found that 41% had experienced some adverse effect irrespective of whether they were taking mefloquine or the combination of chloroquine plus proguanil.5 There was no significant difference between the two regimens in the much smaller proportion of travellers who had either changed or stopped their prophylactic as a result. These authors concluded that about 0.7% of travellers taking mefloquine can expect to have a neuropsychiatric adverse event unpleasant enough to prevent them temporarily from carrying out their day-to-day activities, compared with 0.09% of those taking...
chloroquine and proguanil. This was the only clinically significant difference between the two regimes. Furthermore, the Barrett et al. survey was retrospective whilst the only published survey that combined close prospective observation of a population with certainty as to its size, found that only one of 6000 soldiers taking mefloquine for a mean of 11 weeks suffered any neuropsychiatric effect. However, these subjects were all male while most of the travellers reporting disabling neuropsychiatric events have been women. To the dispassionate observer, it must be clear that disabling neuropsychiatric events after mefloquine are uncommon and, with the rare exception of epileptic seizures, are not associated with any 'hard' neurological signs. However, even sceptical physicians have tended to be persuaded when confronted by complaints of, for example, severe disabling depression or dizziness in subjects whom they knew to have been stable and phlegmatic beforehand.

The UK Consensus Group on Malaria Prophylaxis, which for several years has published annual guidelines on malaria prevention intended primarily for British general practitioners was, therefore, obliged to reach agreement on the strength of data that in almost any other medical context might have been dismissed as largely anecdotal. It has been guided by its Chairman, Professor David Bradley, to a sensible compromise which will probably achieve the best possible balance between protecting travellers from malaria and the adverse effects of medication whilst pragmatically recognizing the reality of consumer-resistance in the UK. For travellers from the UK, mefloquine is now recommended primarily for those visiting West, Central and East Africa for periods of longer than 2 weeks and for those travelling to specific areas within south-east Asia. These travellers are advised to start it 2 weeks before departure in order to increase to 70% the likelihood of picking up adverse events before departure. This will partly answer the concerns that a 1 week run-in period will be insufficient to ensure optimal blood levels during the period when the traveller is at risk. Furthermore, since the risk of adverse events is greatest in the first 3 weeks of taking mefloquine, whereas the risk of malaria is simply proportional to the period of exposure, the risk–benefit calculation favours mefloquine in proportion to the length of time that the traveller is exposed to risk.

The >2 week restriction will also, I believe, answer the recent conclusion to a meta-analysis carried out for the Cochrane Library. This refers to criticisms of the study by Steffen et al. and implies that these criticisms cast doubt on the validity of the study authors’ endorsement of mefloquine versus chloroquine and proguanil. Although both critics were concerned that these authors made insufficient allowance for non-compliance in travellers, one argued that non-compliance would probably have been greater with the more complicated two-drug regimen (which would have led to an over-estimate of the adverse effects of the mefloquine-only regimen) while the other explicitly stated that the results of Steffen et al. were probably correct. The meta-analysis, therefore, adds nothing to the debate and its conclusion that mefloquine is too toxic for prophylactic use remains an opinion which others do not share. In my view the 2 week rule of the UK Consensus Group remains a sensible compromise.

The bulk of British travellers to the area in which most P. falciparum malaria has been acquired will, therefore, henceforth change from a regimen offering 80–90% protection to one offering 70% at best. This new trade-off will only succeed if travellers grasp the importance of their own role in malaria avoidance—which will require a sea-change from the assumption that the ritual of pre-holiday injections etc. means that travellers can relax and put serious infection out of their minds.

The new guidelines incorporate a four-pronged mnemonic for malaria avoidance: A wareness of the risk, B ite avoidance, C ompliance with appropriate chemoprophyllaxis and early D iagnosis of breakthrough malaria leading to prompt treatment. The argument for deliberately abandoning the best prophylactic for the bulk of British travellers at greatest risk of acquiring P. falciparum malaria is based on the fact that, if these travellers are infected, they will develop breakthrough malaria once they are back in the UK and is predicated on the hope that patients and their general practitioners will be aware that influenza-like symptoms appearing within 3 months of return from a falciparum-endemic area necessitate an immediate blood film. Sadly, given human nature and other factors such as the practical difficulty of applying this rule rigorously in influenza epidemics and the less than total sensitivity of blood films, we should anticipate an increase in cases of severe malaria, a proportion of which may end in death.

References

Bacterial vaginosis (BV) is the commonest cause of abnormal vaginal discharge in women of childbearing age. The prevalence in the UK is between 10 and 15%. The principal symptom is an offensive fishy smell, accompanied by an increased vaginal discharge. When BV develops, the concentrations of many anaerobic or facultative anaerobic species, including Gardnerella vaginalis, Bacteroides spp. and Mycoplasma hominis, increase up to a thousand-fold, overwhelming the usually dominant lactobacilli. In the most severe forms of BV the lactobacilli disappear. The bacteria adhere to desquamated squamous epithelial cells, giving them the appearance of ‘clue cells’. The pH of vaginal fluid increases from the normal, <4.5, to as high as 7.0. The term bacterial vaginosis was adopted in 1983, the word ‘bacterial’ to indicate that many bacterial species are present, and the suffix ‘-osis’ because inflammation is absent. Some clinicians use alternative terms such as anaerobic vaginosis, non-specific vaginosis or even ‘gardenella’.

The aetiology of BV is unknown. It has some characteristics of a sexually transmitted disease (STD) and, in some studies is associated with STDs such as chlamydia, gonorrhoea and pelvic inflammatory disease (PID). It often develops in women with trichomoniasis. BV is more common in women of black race, those who have an intrauterine contraceptive device (IUCD) and those who smoke. In a prospective study BV was also found to be more likely to develop if a woman changed her sexual partner or practised vaginal douching or cunnilingus. The prevalence is high among lesbian women, a group with a low incidence of traditional bacterial STDs. The high concordance rate of lesbian couples to have or not have BV can be interpreted as evidence of sexual transmission between women. Against the concept of sexual transmission however, is the study in which clue cells, as evidence of BV, were detected in 5% of reportedly virgin adolescent schoolgirls in the USA.

BV may develop and resolve spontaneously within a few days. Prospective studies employing daily Gram-stained vaginal smears have shown that in some women the vaginal flora is in a very dynamic state. BV develops most often around the time of menstruation, and resolves mid-cycle. Hormonal influences may therefore be critical in the control of the vaginal flora. It is often stated that unprotected sexual intercourse is a trigger for BV. One study, however, found that unprotected sexual intercourse with a regular partner was associated with resolution of BV, and it may be that the presence of semen increases the vaginal odour of BV, making women more aware of its presence following intercourse.

The frequency of relapses, particularly at the time of menstruation, affects the results of treatment trials. A study in which the first follow-up evaluation is performed before the next menstrual period is likely to show a higher rate of cure than one in which women are assessed following their next menstruation. Follow up for more than 1 month is difficult to achieve, without an unacceptably high drop-out.

Studies vary in their definitions of BV and cure. Most treatment studies use the Amsel criteria for the diagnosis of BV. This requires that at least three of four criteria are fulfilled: (i) pH of vaginal fluid >4.5; (ii) clue cells present; (iii) characteristic homogeneous vaginal discharge; and (iv) fishy odour on addition of alkali to a sample of vaginal fluid. Some studies require that no more than two criteria are fulfilled: (i) pH of vaginal fluid >4.5; (ii) clue cells present; (iii) characteristic homogeneous vaginal discharge; and (iv) fishy odour on addition of alkali to a sample of vaginal fluid.