Key messages

- Uncertainty persists about the frequency of adverse neurological and psychiatric events associated with the antimalarial drugs mefloquine and proguanil plus chloroquine
- This study shows that about 40% of travellers taking either mefloquine or chloroquine and proguanil can expect to experience some sort of adverse side effect, although most side effects will be relatively trivial
- About 0.7% (1 in 140) travellers taking mefloquine can expect to have a neuropsychiatric adverse event unpleasant enough to temporarily prevent them from carrying out their day to day activities, compared with 0.09% (1 in 1100) taking chloroquine and proguanil
- Mefloquine is appropriate only when the risk is high both of malaria and of chloroquine resistance

Thus nine (0.7%) subjects had disabling neuropsychiatric side effects after taking mefloquine. Overall, 21 (1.7%) subjects had unpleasant or disabling neuropsychiatric side effects of any grade after taking mefloquine.

Among the 12 users of proguanil plus chloroquine, one was lost to follow up, and, in six cases, the referees agreed that the side effects were unrelated to the use of proguanil plus chloroquine or were not neuropsychiatric in nature. One respondent (0.09%) was deemed to have had a disabling neuropsychiatric side effect associated with the use of proguanil plus chloroquine (table 2), and an additional four were considered to have had unpleasant but not disabling neuropsychiatric side effects (overall, 0.4%). The rates for disabling ($P = 0.02$) and combined ($P = 0.004$) neuropsychiatric side effects differed significantly between the two regimens, but the rates for unpleasant effects did not ($P = 0.09$).

If we take as the denominator the number of non-respondents advised to take each regimen then 0.5% (9/2006) of those advised to take mefloquine and 0.07% (1/1491) of those advised to take proguanil plus chloroquine had disabling neuropsychiatric side effects ($P = 0.05$). Unpleasant but not disabling neuropsychiatric side effects were experienced by 0.6% (12) of those advised to take mefloquine and by 0.3% (4) of those advised to take proguanil plus chloroquine ($P = 0.2$). Overall, 1.1% (21) of those advised to take mefloquine and 0.3% (5) of those advised to take proguanil plus chloroquine had either unpleasant or disabling neuropsychiatric side effects ($P = 0.03$).

Discussion

The results show how relative frequencies of adverse events vary, depending on the criteria used. The frequency of discontinuing or changing chemoprophylaxis was the same for proguanil plus chloroquine and mefloquine. The frequency of "serious" adverse events (as defined by the criteria of the Council for International Organisations of Medical Sciences) that were apparently related to chemoprophylaxis was one case for proguanil plus chloroquine and two for mefloquine, each in a population of around 2300. Though these rates are suggestive of rates higher than 1 in 10 000, the study is too small to generate accurate data on rates of very rare events.

The most prominent differences in self reported adverse events between the two regimens are in the neuropsychiatric category, where adverse events with mefloquine categorised by the traveller as "bad enough to interfere with daily activities" (9.2% of users) or "bad enough to make you seek medical advice" (2.2%) were each about twice as common as with proguanil plus chloroquine. Overall, 11.8% of people taking mefloquine had adverse neuropsychiatric events of grade 2 or worse. When histories were taken from respondents with self reported grades 3 and 4 and evaluated, nine people (0.7%) taking mefloquine and one person (0.09%) taking proguanil plus chloroquine had temporarily disabling neuropsychiatric symptoms.

It therefore seems that, although the proportion of people abandoning the regimen is the same for mefloquine and proguanil plus chloroquine, and "serious" side effects are rare with each, there is a significantly raised frequency of neuropsychiatric side effects in those taking mefloquine. It seems that these side effects are experienced as disabling or very upsetting by those affected. These observations provide an explanation for the discrepancy in results from published surveys and reported clinical anecdotes.

This study concentrated on one group of adverse events in an attempt to shed light on a specific issue. It did not cover every aspect of adverse events in the same detail nor has it examined prophylactic efficacy—for which larger populations would be needed—and therefore addresses only one aspect of the choice of regimens for travellers. The findings of this study are, however, consistent with clinical impressions in Britain and will tend to favour the view that mefloquine is appropriate only where the risk is high both of malaria and of chloroquine resistance.

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Adverse local reactions from accidental BCG overdose in infants

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Local reactions to BCG vaccine depend on the administration technique, the dose, and the type of BCG preparation.[1] We report on infants who were accidentally vaccinated intradermally with a percutaneous BCG preparation, receiving about five times the upper limit of the currently recommended intradermal dose of BCG.

Methods and results

All infants born at our hospital before November 1994 were routinely given intradermal BCG after written parental consent was obtained. A total of 857 infants were accidentally vaccinated intradermally with the percutaneous BCG (Evans E4981A and E4946B) between July and November 1994. After public announcement of the error, 556 of these infants attended special follow up clinics where they were examined for adverse reactions to BCG.

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The median age at vaccination was 10 days (range 1-403 days). Infants were seen at the clinic a median of 65 (7 to 139) days after vaccination. A total of 61 infants (11.0%) had adverse local reactions. Forty eight infants (8.6%) had axillary lymphadopathy; one had an axillary lymph node >20 mm in diameter. Six infants had papules >10 mm diameter, and another six had ulcers >10 mm diameter. In one infant an abscess at the injection site was aspirated by needle.

One infant who received this BCG at 6 weeks of age presented at 4 months with severe combined immune deficiency (Omenn syndrome). She was treated with anti-tuberculosis drugs until her death from pulmonary haemorrhage after a bone marrow transplant. A lung biopsy three days before her death did not show histological changes of disseminated BCG.

Comment

The definition of an adverse local reaction to BCG varies greatly. O'Brien *et al* consider axillary lymph nodes >20 mm or vaccination ulcer prolonged for more than six weeks to be mild complications, axillary abscess or fistula to be moderately severe complications, and disseminated BCG infection to be severe complications.[2] By these criteria only one child in our study had a mild reaction.

In older children, a normal BCG ulcer should not exceed >10 mm in diameter and should heal within four weeks.[3] Six of our infants (1.1%) had ulcers >10 mm diameter, but this may be an underestimate as the infants were examined at different times after their vaccination. The size of the BCG ulcer depends on the technique of vaccination as much as the dose. In one report 158 of 403 children vaccinated by a doctor developed adverse local reactions; this was attributed to faulty technique.[3] The low adverse local reaction rate in our cohort may, despite the high dose of BCG used, reflect the experience and good intradermal vaccination technique of the two doctors who administered the vaccine.

Surprisingly, the patient with Omenn syndrome did not show evidence of disseminated BCG infection. This syndrome in its early stage is characterised by polyclonal proliferation of T lymphocytes, and we speculate that these T lymphocytes may have been capable of activating macrophages, thus preventing dissemination of BCG in this patient.

While human error was responsible for this "accident," it is important to note that the ampoules, packaging, and labelling of the Evans intradermal and percutaneous BCG preparations are deceptively similar. Distinctive labelling and packaging of the intradermal and the percutaneous BCG preparations would have helped to draw attention to their different potency.

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Family members' attitudes toward telling the patient with Alzheimer's disease their diagnosis

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Advances in the accuracy of the diagnosis of Alzheimer's disease as well as progress in the genetics, aetiopathology, and therapeutics of the condition have stimulated a debate on whether patients should be informed of their diagnosis. We report the results of a survey of family members on their attitudes to the disclosure of the diagnosis.

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Patients, methods, and results

A total of 100 consecutive family members accompanying patients with diagnosed Alzheimer's disease to a memory clinic were asked three questions by the assessing physicians (CPM, MK): should the patient with Alzheimer's disease be told their diagnosis; would they themselves want to be told their diagnosis should they develop Alzheimer's disease; and would they make use of a predictive test for Alzheimer's disease should it become available? They were also asked to state the reasons for their decisions.

Only 17 family members said that the patient should be told the diagnosis; 83 said that they should not. The main reason given was that the diagnosis would upset or depress the patient (table 1). In contrast, 71 family members wanted to be told their diagnosis should they develop Alzheimer's disease; most stated that it would be their right to be told their diagnosis. Seventy five family members would use a predictive test for Alzheimer's Disease; 42 of these said it would give them the opportunity to make provisions for their future and thereby reduce the burden on their families.

Comment

The majority of relatives of patients with Alzheimer's Disease would not want the patient told the diagnosis, but would themselves wish to know if they developed the condition. This inconsistency may reflect a generational difference in the perception of the disease, apaternalistic desire by family members to protect patients from the harsh reality of their condition, or a reluctance of relatives to deal with the patient's knowledge and possible grief.

Most of those who opposed disclosure of the diagnosis to the patient felt that it could precipitate symptoms of anxiety and depression. However, Bahro *et al* have shown that when the diagnosis is given, both patients and family members often use denial as a defence mechanism to deal with it.[2] Many patients are aware of their progressive cognitive deficits, regardless of whether or not a diagnosis of Alzheimer's disease has been given. Insight may be an important determinant of reaction to disclosure, with lack of insight providing a degree of psychological protection. Retention of insight varies from patient to patient and seems unrelated to degree of cognitive deterioration.[3] In insightful patients, the risk of depressive reactions or even suicide must be seriously considered after disclosure of any major illness. This seems no different in Alzheimer's disease. Two cases of suicide in patients told their diagnosis have recently been described.[4] In our study, 10 family mem-