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Because we receive many more letters than we have room to publish we may shorten those that we do publish to allow readers as wide a selection as possible. In particular, when we receive several letters on the same topic we reserve the right to abridge individual letters. Our usual policy is to reserve our correspondence columns for letters commenting on issues discussed recently (within six weeks) in the BMJ.

Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue. We may also forward letters that we decide not to publish to the authors of the paper on which they comment.

Fansidar in malaria prophylaxis

SIR,—There is confusion over the use of the fixed drug combination containing pyrimethamine 25 mg and sulphadoxine 500 mg and marketed as Fansidar in the prophylaxis of malaria, and this letter sets out the present position as perceived by the Malaria Reference Laboratory.

In areas endemic for chloroquine resistant falciparum malaria and where the risk of exposure to infection is great the choice of malarial prophylaxis is difficult. In general, the safe drugs give limited protection and the more effective prophylactics can cause toxic side effects. The two drugs in the latter category used in the UK are Fansidar and Maloprim (Maloprim is a fixed dose combination of pyrimethamine 12·5 mg and dapsone 10 mg).

The rare but severe toxic side effects of Fansidar are those of its sulphonamide component and comprise Stevens-Johnson syndrome and toxic epidermal necrolysis. Concern was aroused by a recent review of experience in the USA, which showed a mortality of between 1 in 18 000 and 1 in 26 000 from Fansidar taken as a prophylactic against malaria, an unacceptably high level under most circumstances. No published data are available for the frequency of side effects outside the USA, but available evidence suggests that the complication rate may be much lower in parts of the continent of Europe, although the rate in the UK is closer to the American rate. The continental complication rate appears tolerable, the American (and British probably) does not. The basis for the observed differences could conceivably be genetic, or caused by ascertainment bias or reporting artefact, or due to confounding with another variable. One proposed confounding factor is the concurrent administration of chloroquine.

Because Fansidar has some limitations as a prophylactic against *Plasmodium vivax* it has been usual in the USA, and to some extent in the UK, to recommend the concurrent use of chloroquine and Fansidar for travellers. This is not usual on the Continent. The increased incidence of toxic complications might therefore be ascribed with some plausibility to this drug combination; and there is more direct evidence from a small scale comparative trial in which the frequency of cutaneous side effects was much higher when Fansidar was given with chloroquine than when Fansidar and mefloquine were administered.

We therefore recommend that Fansidar should not be prescribed concurrently with chloroquine for prophylaxis against malaria. As an alternative proguanil or Maloprim, given together with amodiaquine or chloroquine, is at present a possible prophylactic for chloroquine resistant falciparum malaria in high risk areas. Broader issues of prophylaxis will be dealt with by a meeting of experts shortly.

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1 *WHO Weekly Epidemiological Record* 1985;**60**:181-8.

"Missed pill" conception: fact or fiction?

SIR,—We were interested in the article by Dr B G Molloy and others (18 May, p 1474), since one of us (JG) has been emphasising the importance of the pill free week in the causation of missed pill conceptions for some years.[1] In a study using volunteers from this centre (and surprisingly not referenced by the authors) we showed that ovarian 17-β oestradiol concentrations tend to rise during the pill free time. In some women the values measured were similar to those associated with a preovulatory follicle.[2] What Dr Molloy and colleagues have now shown is that ovarian folliculogenesis parallels this rise in endogenous oestradiol and is similarly very pronounced in some apparently normal pill takers.

We agree with the authors' view that in such women missing pills at the beginning of a subsequent packet is likely to lead to ovulation. But we would add that there can be an entirely similar situation if a woman omits some pills at the end of the previous packet but still starts the next one after a further seven days (on her usual starting day). This will similarly lengthen the pill free time. We are conducting further studies to measure endogenous and exogenous hormones as well as observe follicular activity by ultrasound. Volunteers are asked to omit tablets deliberately before as well as after the pill free week.

Dr Molloy and colleagues rightly emphasise that women should be warned of the danger of delaying restarting treatment after the seven pill free days. Twenty three day packaging as proposed, followed by five placebo tablets, would certainly be useful for some women, especially those on hepatic enzyme inducing drugs. But it is less clear that there should be routine use of such a regimen, since this would increase (by 10% each month) the number of days of exposure to artificial steroids.