

# Reports on Individual Drugs

## Antimalarials in pregnancy

**Nigeria** — Repeated attacks of malaria during pregnancy result in placental insufficiency and women exposed to infection are at high risk — particularly during their first pregnancy — of delivering premature or low-birth-weight infants (1). Chloroquine provides effective protection against *Plasmodium falciparum* infections in those areas where the parasite remains susceptible, but chemoprophylaxis is more problematic where there is a high prevalence of chloroquine resistance.

Pyrimethamine is still widely used, on the basis of encouraging findings obtained in the mid-1960s (2), to protect pregnant women from malaria in some areas of West Africa. Even at that time the emergence of resistant strains of *P. falciparum* had been reported in the vicinity (3, 4) and data assembled within the past two years in south-west Nigeria show that some two-thirds of the women now presenting there with parasitaemia do not benefit from the generally used weekly suppressive prophylactic dosage of 25 mg pyrimethamine (5). Nor does this regimen reduce the relapse rate among women who first receive a curative course of chloroquine.

The use of pyrimethamine in pregnancy also raises considerations of safety. As an inhibitor of dihydrofolate reductase it is a presumptive teratogen (6, 7) and it has been shown to induce malformations when administered experimentally at high dosage to rats (8). This has prejudiced its administration to pregnant women, during the first trimester, in the relatively high doses required in the preventive management of congenital toxoplasmosis (9). No evidence has been adduced to indicate that exposure to pyrimethamine has caused malformations in human fetuses when it is used prophylactically, either as an antimalarial (10) or in toxoplasmosis (11, 12). There is no way, however, to exclude the possibility that drugs may have contributed to the occasional malformations inevitably encountered in such surveys.

Knowledge that pyrimethamine has long been used as an antimalarial in circumstances in which it may have been largely ineffective, at least in the area

of west Africa where the recent survey was undertaken, provides a vivid illustration of the vital and ubiquitous need, so effectively portrayed by Professor Calvin Kunin elsewhere in this issue (page 4), to develop an infrastructure in all countries for effective and open-ended monitoring of the performance not only of antibiotics, but of all widely used chemotherapeutic agents.

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### Acetylsalicylic acid: adverse effects or artefact?

A recently published prospective study that examines the association between regular use of acetylsalicylic acid and various chronic diseases has attracted considerable comment in both the professional and lay press (1). The information on which it is based was obtained through serial postal questionnaires concerned with a broad range of issues relating to life-style and disease prevention that was directed to some 22 000 residents living in a retirement community in California. Incidences of cardiovascular diseases, cancers, gastrointestinal bleeding, ulcers and cataracts were compared in participants who either did or did not take acetylsalicylic acid daily. The broad conclusions were that daily use of acetylsalicylic acid increases the risk of renal cancer and ischaemic heart disease, but both findings have aroused sharp critical reaction.

Combing a given data set in search of statistically significant associations that were not necessarily entertained when the study was planned is very likely to yield a number of chance findings. Some of these may not be soundly based simply because the study was not designed to address every consideration critical to their analysis. For instance, this particular study has been criticized (2) because there is no way of establishing from the published account whether any of the patients who developed renal cancer after taking acetylsalicylic acid daily for an unspecified period of time had also taken other analgesics — and particularly phenacetin, an established carcinogen — on an habitual basis. Similarly, the claimed association between acetylsalicylic acid and ischaemic heart disease could merely reflect that patients at risk of death from cardiovascular disease may be particularly likely to take the drug habitually as an analgesic. Indeed, this possibility has been confirmed in studies suggesting that acetylsalicylic acid may provide appreciable protection against ischaemic heart disease (3, 4).

The time is fast approaching, perhaps, when all groups active in this complex and sometimes contentious field should seek to develop a consensus on the criteria that need to be satisfied when a pharmacoepidemiological study is prepared for publication, and particularly the considerations that

need to be given to the ever-present problem of confounding bias.

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### Chloroquine abuse and heart block

**Nigeria** — Taken at the dosages recommended for the treatment and prophylaxis of malaria, chloroquine is an exceptionally safe drug. A risk of retinal damage (1-3) or, in rare instances, of neuromyopathy (4) occurs only as a consequence of prolonged daily use at much higher dosages. In contrast, the acute toxicity of chloroquine is dramatic. A single overdose of 5 g generally results in fatal cardiac arrest within three hours (5). Recent claims suggest that early mechanical ventilation and administration of diazepam with either dopamine or adrenaline — and even charcoal haemoperfusion — may save some patients (6, 7) but, otherwise, attempts at treatment have been largely ineffective.

Less has been written concerning the possible hazards of chronic chloroquine abuse, although this is an inescapable problem in malarious areas where self-medication is common and chloroquine is often taken without supervision to treat virtually any febrile condition. Isolated reports have suggested that this practice may sometimes result in heart block (8-10) and this suspicion has now been confirmed in a survey of 30 patients presenting with this condition at a teaching hospital in Nigeria (11). Twelve were discovered to have been taking chloroquine in varying degrees of excessive dosage over periods of 2 to 10 years and all but one were found to have moderate to severe chloroquine retinopathy. Based on this evidence, it seems important to ask every patient presenting in a malarious area with atrio-ventricular block of uncertain cause about their use

of chloroquine, regardless of whether it is prescribed or bought over-the-counter.

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## Intramuscular chloroquine and quinine: a reappraisal

**Gambia** — Intravenous infusion of quinine has long been regarded as the most effective treatment for severe falciparum malaria. However, many patients are first seen in rural health clinics where it is either impracticable or impossible to set up infusions. Necessity then demands that the drug be delivered

either by intravenous or intramuscular injection. Unduly rapid intravenous injection of quinine can sometimes result in fatal hypotension (1, 2) while concern regarding localized muscle necrosis and abscess formation has discouraged intramuscular delivery. Analogous problems are associated with the use of parenteral chloroquine which WHO has disfavoured on grounds of cardiovascular toxicity (3, 4). None the less, it has been claimed in several recent studies to be as effective as quinine in uncomplicated drug-sensitive infections (5-7), and there is now doubt as to whether the hazards of intramuscular injection of either compound at the dosages now recommended are as great as was previously assumed (8-10).

In an attempt to resolve these uncertainties and, in particular, to reappraise the safety of intramuscular administration, 50 Gambian children with severe falciparum malaria have recently been studied in an open, randomized trial in which they were allocated to receive by the intramuscular route either 3.5 mg/kg chloroquine base as the sulphate every six hours or 20 mg/kg quinine hydrochloride every 12 hours (11). Eight of the children died from malaria, notwithstanding treatment. Of these, six had received quinine. This, it is thought, does not necessarily denote any difference in efficacy between the two drugs, despite clear evidence that parasitaemia tended to clear more rapidly among the children receiving chloroquine. Moreover, whereas quinine injections were obviously painful, chloroquine injections were not. Neither treatment resulted in severe systemic toxicity, although quinine may have induced or exacerbated hypoglycaemia in three patients, indicating that a need for dextrose infusion should be anticipated when it is used.

In their conclusion the authors seek to dispel some of the concerns that have been associated with parenteral use of chloroquine in the past. They emphasize that only high-grade resistance precludes use of chloroquine in the treatment of severe falciparum malaria and they challenge much contemporary teaching by asserting that, where chloroquine can be used, it is «probably as effective, less locally toxic, cheaper, and more rapidly acting than quinine».

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## Acetylsalicylic acid and eclampsia

Recognition within the past few years that acetylsalicylic acid has a significant thrombolytic action has impressively extended its therapeutic applications. Most recently, it has been confirmed that doses of as little as 60 to 100 mg daily taken from the twelfth week — or even the twenty-eighth week — of

pregnancy can significantly reduce the extent of pre-eclampsia, and of fetal growth retardation and perinatal death associated with pregnancy-induced hypertension (1-4). This appears to result from reduced synthesis by platelets of a prostaglandin-like substance, thromboxane A, which is thought to induce the vasospasm, ischaemia and thrombosis associated with pre-eclampsia (5).

It has been estimated that, in some settings, as many as 20 per cent of women develop a degree of hypertension during their first pregnancy and that a substantial proportion of these also have proteinuria (6). Not surprisingly, the use of low-dose acetylsalicylic acid is already being canvassed in the routine management of these pregnancies (3, 4). However, fewer than 100 women have as yet been studied and more needs to be known about the effects of these doses of acetylsalicylic acid on haemostasis in both mother and fetus before the routine application of these findings to a substantial proportion of pregnant women can be entertained. It has been conceded, however, that a strong rationale now exists for treating the smaller number of women at greatest risk of eclampsia (7).

An important point of concern is that, although exposure to acetylsalicylic acid during pregnancy has not been shown to increase the overall incidence of congenital malformations (8, 9), suggestions have been raised that it may augment the risk of specific cardiac defects, including aortic stenosis, coarctation of the aorta, hypoplastic left heart, and transposition of the great arteries (10, 11). However, a recently published case-control evaluation of almost 1400 infants notified as having any form of structural cardiac defect (12) has failed to demonstrate any significant association between exposure to acetylsalicylic acid — as determined during an interview conducted within a few months of delivery — and any specific defect. Nor was any suggestion of a dose-effect pattern identified. The balance of evidence regarding the possible teratogenic potential of acetylsalicylic acid now seems to be firmly reassuring.

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## Dangers of antidiarrhoeal drugs

**Pakistan** — Paediatricians from the Nishtar Medical College have written to the *Lancet* to offer dramatic first-hand evidence of the potentially grave consequences of misconceived use of antidiarrhoeal drugs in infants with acute watery diarrhoea. They claim that in the last two months of 1989 no less than 19 children were admitted to their service with severe abdominal distension and paralytic ileus after having received the anti-cholinergic agent, loper-

amide, in dosages of 1 to 6 mg per day. Over half of them died and in no case was any other cause of death apparent.

The authors concede that the package bears a warning indicating that the drug should not be used in children less than one year of age, but they challenge manufacturers to explain what protection this provides "...where drugs are freely available over the counter, where 99 per cent of patients cannot read, and where unqualified people use drugs without knowing the side-effects".

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## Melarsoprol encephalopathy: the preventive effect of corticosteroids

**Zaire** — Melarsoprol, a trivalent arsenical derivative, remains the only generally available trypanocidal drug which crosses the blood-brain barrier. Until more effective agents are developed — eflornithine (alpha-difluoromethylornithine) has already shown considerable promise (1) — it offers the only hope of preventing death in the late stages of African trypanosomiasis. However, it is arguably the most dangerous drug in routine use, since up to ten per cent of patients die from drug-induced encephalopathy (2). Although corticosteroids have long been widely used with a view to reducing mortality, no trial of adequate size has been conducted to confirm their value (3).

This uncertainty has now been dispelled by a prospective randomized trial involving some 600 patients with parasitologically-confirmed *Trypanosoma brucei gambiense* infections (4). Each received a preliminary dose of suramin to reduce peripheral parasitaemia. From 6 to 12 intravenous infusions of melarsoprol, each containing a dose of 3.6 mg/kg to a maximum of 200 mg, were then administered having regard to the cell content of the cerebrospinal fluid. No more than three to four infusions were given on consecutive days and the courses were punctuated by a treatment-free interval of one week on the first occasion and for two weeks on subsequent occasions. Half the patients additionally received prednisolone at a maximum dose of 40 mg daily throughout the period of treatment, except for the two-week treatment-free intervals. No placebo was used. Arsenical encephalopathy was diagnosed if impaired consciousness, seizures or abnormal behaviour occurred *de novo* subsequent to the first dose of melarsoprol.

The results were clear-cut. More than a third of the patients in the control group, but only 4 per cent of those given corticosteroids, developed encephalopathy and over half of these patients died. No difference was detected between the two groups in the incidence of other complications of melarsoprol therapy. Nor was there any significant difference in the relapse rates among survivors.

The authors are confident that their results are also valid for *T. b. rhodesiense* infections and they recommend that prednisolone should now be given empirically to all patients receiving melarsoprol for sleeping sickness. They warn of the need to treat or to exclude other parasitic infections, particularly strongyloidiasis and amebiasis, before corticosteroids are given. They also point to the cost-effectiveness of steroid therapy in these circumstances. The cost of the prednisolone for a typical patient represents a surcharge of only some three per cent on the cost of a course of melarsoprol, an investment that is offset many times over by savings resulting from the decreased incidence of encephalopathy.

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### Mortality trends among users of oral contraceptives

**United Kingdom** — As the first generation of women to have used combined steroidal oral contraceptives passes through the middle years of life, data on which to base a meaningful assessment of the consequential long-term effects, both benefi-

cial and harmful, are fast accumulating. Some disconcerting results indicating that overall mortality might be some 40 per cent higher among former users emerged from data assembled ten years ago in the United Kingdom (1). The excess deaths were largely attributable to an increased incidence of cardiovascular disease, which had already been independently associated with the use of oral contraceptives (2-4). However, despite their plausibility, the findings were met with some scepticism. It was pointed out that they were inconsistent with vital statistical trends (5, 6) and that most of the exposure was to preparations containing relatively high dosages of estrogen that had subsequently been withdrawn from general use.

Recently published interim results of an independent prospective survey of some 17 000 British women who have already been followed for 20 years are considerably more reassuring. The data, as they stand at present, provide no suggestion that use of oral contraceptives has any influence on overall mortality but, since only 238 of women within the cohort had died when the analyses were undertaken, it is possible that unanticipated trends and associations may yet emerge (7). None the less, several trends in the relative incidence of specific diseases within the cohort are consistent with the findings of other groups: notably, positive associations for carcinoma of the cervix and for ischaemic heart disease and an apparent protective effect against ovarian carcinoma.

As yet, these estimates are derived from very small numbers of cases. Highly impressive, however, even at this stage, is the apparent interactive effect of oral contraceptive use and cigarette smoking as a risk factor in cardiovascular disease (see also page 29). Eighteen women within the cohort have already died of ischaemic heart disease, 17 of these were smokers and 15 had used oral contraceptives at some time in the past.

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## Management of ulcers induced by NSAIDs: costs and benefits

**United Kingdom** — The potential of acetylsalicylic acid to cause peptic ulceration has been recognized for more than 50 years (1). It is now apparent that this is a problem associated with nonsteroidal anti-inflammatory agents in general (2) and resulting in some 200 deaths each year in the United Kingdom alone (3). Inevitably, possible preventive measures have evoked much attention, including pharmacological intervention to reduce the acidity and proteolytic activity of the gastric fluids. The synthetic prostaglandin, misoprostol, is reported — on the basis of a controlled multicentre study — to markedly reduce the incidence of drug-induced gastric ulcer (4), while the H<sub>2</sub>-receptor antagonist, ranitidine, offers similar protection against drug-induced duodenal ulcer (5). Ranitidine, it is claimed, has not been shown to protect against gastric ulcer, and there is insufficient information to establish the effect of misoprostol on duodenal ulcers induced by these drugs (2).

A recent review article in the *British Medical Journal* (2) questions "whether doctors should use misoprostol to prevent the gastric ulcers, ranitidine to prevent the duodenal ulcers, or both at double the cost". The author estimates that 22 million prescriptions for an average of 30 days supply of a nonsteroidal anti-inflammatory drug are written in the United Kingdom each year and that the annual cost of co-prescribing misoprostol or ranitidine with each of them would approximate to some US\$ 750 million. This being so, and even if these two products were totally effective in preventing deaths from drug-induced ulceration, the cost of saving each life would be of the order of US\$ 4 million (3).

A further series of questions devolves from these estimates. Would such costs, or the likely incidence of yet other adverse effects generated by such massive co-prescribing, justify the benefits achieved? Would acid-inhibiting drugs be as effective as misoprostol if higher doses were used? Clear answers can only be obtained, the article emphasizes, when more determined efforts have been made to identify groups of patients at particular risk; to explore whether, as seems probable, protection is most needed at the outset of treatment with non-steroidal anti-inflammatory drugs before adaptive changes have occurred in the gastric mucosa (6-8); and to compare directly the effects of optimal doses of misoprostol and an acid-inhibiting drug.

Answers to these questions can only be provided by large prospective controlled studies that will require considerable organization and funding. The same dilemma arises time and again in the evaluation of prophylactic therapy, but if priorities in health care are to be determined on grounds of cost-effectiveness, the evidence required for sound decision-making must be forthcoming.

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association of non-steroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding. *Archives of Internal Medicine*, **147**: 85-88 (1987).

### Chloroquine: resistance reported in *Plasmodium vivax*

*Plasmodium vivax* is the most widespread of the malarial parasites and is responsible for much chronic debilitating illness. Until recently, its control had been considerably facilitated because, unlike *P. falciparum*, it has remained reliably susceptible to chloroquine. Concern has recently been raised, however, that a strain of *P. vivax* may be emerging in Papua New Guinea with reduced chloroquine sensitivity (1). Parasites were not suppressed in two soldiers who had been taking 300 mg chloroquine base, 12.5 mg pyrimethamine, and 100 mg dapsonone once a week for 7-9 weeks. Both presented with parasitaemia and signs typical of acute malaria at a time when their plasma chloroquine concentrations were considerably higher than 15 nanograms per ml, a level generally regarded as an effective therapeutic concentration against *P. vivax* (2).

Since at least three other cases of *P. vivax* infection contracted either in Papua New Guinea or the Solomon Islands seem not to have responded adequately to chloroquine, a need is clearly evident for clinicians to remain alert to the possibility of chloroquine resistance everywhere that *P. vivax* is endemic. It is vital, however, that reports of resistance should be securely based and that the case records should include not only precise estimates of plasma chloroquine concentrations but also laboratory confirmation of the identity of the responsible parasite.

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### Chemotherapy and secondary leukaemia

It was first noticed almost 20 years ago that patients

who survive for some years after intensive anti-cancer chemotherapy are at increased risk of developing acute leukaemia (1) and there is now little doubt that this results largely from chromosomal damage inflicted by alkylating agents (2). Characteristically, chromosomes 5 and 7 are partially or completely missing in the malignant cells of patients with secondary leukaemia (3) and it seems that the most critical region for this damage is a segment of the long arm of chromosome 5. Recently, this has been shown to be the locus of genes that encode for granulocyte-macrophage colony stimulating factor and several interleukins that regulate the growth and differentiation of haematopoietic stem cells (4).

It has been difficult, none the less, to establish a causal relationship with certainty because of the possibility, amongst others, that long-term survivors of the primary malignancy are inherently at increased risk of developing acute leukaemia. However, persuasive evidence that chemotherapy is responsible for the excess risk was provided in 1987 by an analysis of the records of 87 000 survivors of ovarian cancer identified in 11 population-based cancer registries (5). One-quarter of the patients had been treated with surgery alone and, among these, the incidence of acute or nonlymphocytic leukaemia was similar to that expected in a population of healthy women of comparable age. The incidence was approximately twelve-fold higher among a rather smaller proportion of the patients who had received chemotherapy alone and the risk was greatest some four to six years after the exposure.

Using the case-control technique, the same research group has since examined the relative risks associated with different forms of chemotherapy in women with ovarian carcinoma (6) and patients with Hodgkin's disease (7). A search of records contained in selected cancer registries and specialized institutions in North America and Europe yielded 114 cases of leukaemia among some 100 000 patients previously treated for ovarian cancer and 163 similar cases among some 30 000 patients treated for Hodgkin's disease.

The results obtained in the ovarian cancer study were consonant with those obtained earlier. A highly significant association was established both for the widely-used combination of doxorubicin hydrochloride and cisplatin and for five other compounds when used alone — chlorambucil, cyclophosphamide, melphalan, thiotepa and treosulfan.

About 1 in 200 patients treated with chemotherapy alone for Hodgkin's disease developed leukaemia within the next decade. Among those treated exclusively with radiotherapy the risk was some nine-fold less. The cases, which peaked five years after exposure, were most frequent among younger patients, those treated with higher dosages, those with more advanced disease at diagnosis, and those who had undergone splenectomy. A marked positive dose-relationship was apparent among patients treated with mechlorethamine and procarbazine, but too few had been treated exclusively with the more recently-introduced combination of doxorubicin, bleomycin, vinblastine and dacarbazine to support any estimate of associated risks.

Notwithstanding these findings, the prospect of cure that chemotherapy offers in Hodgkin's disease vastly outstrips the small risk of consequential leukaemia (8). Although the corresponding risk for patients with ovarian cancer is several-fold less, the data that have been generated may have more immediate implications for the treatment of this condition. The authors point to evidence that the association is dose-related yet, with the exception of recent and unconfirmed experience with melphalan and doxorubicin (9), there is no firm evidence that use of more intensive regimens increases the prospect of survival in these patients.

By conducting two independent and mutually supportive studies directed to the same problem the authors have generated some singularly persuasive evidence that serves to validate their methods as well as their findings. Not least, they have demonstrated the importance and the feasibility of generating statistically secure data on the long-term effects of anticancer chemotherapy in disease-specific contexts from readily-accessible information.

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#### Parenteral quinine: an essential drug

United Kingdom — In recent years up to 2000 cases of malaria have been reported annually within the United Kingdom among travellers infected abroad (1) and over the past decade the number of reported cases of *Plasmodium falciparum* infection has increased three-fold (2). Seriously ill patients with *falciparum* malaria require emergency parenteral treatment with quinine, yet a recent nationwide survey indicated that no injectable formulation was available in the pharmacies of 20 per cent of the acute-care hospitals within the country (3). Some two-fifths of the pharmacies that held stocks had received requests for supplies within the previous two years, and the principal conclusion drawn from the survey is that injectable quinine should be