Serious adverse drug reactions to pyrimethamine-sulphadoxine, pyrimethamine-dapsone and to amodiaquine in Britain

P A Phillips-Howard PhD *Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT*
L J West PhD *Committee on Safety of Medicine, Department of Health, London SW8 5NQ*

Keywords: adverse drug reactions; pyrimethamine-sulphadoxine; pyrimethamine-dapsone; amodiaquine

Summary

All reports of adverse reactions with pyrimethamine-sulphadoxine (Fansidar), pyrimethamine-dapsone (Maloprim), and amodiaquine spontaneously reported through the UK national post-marketing system were reviewed. Retrospective reporting rates of serious reactions associated with these drugs were analysed using prescription data from the Department of Health, derived from the Prescription Pricing Authority, and relevant pharmaceutical companies. Whilst interpretation of these data requires caution, they allowed comparison with reporting rates from other studies. The reported rate for all serious reactions to pyrimethamine-sulphadoxine was 1 : 2100 prescriptions, and for cutaneous reactions was 1 : 4900 prescriptions, with a fatality rate of 1 : 11 100. The reported rate for serious reactions to pyrimethamine-dapsone was 1 : 9100 prescriptions, and for blood dyscrasias was 1 : 20 000 prescriptions, with a fatality rate of 1 : 75 000. The reported rate of blood dyscrasias associated with amodiaquine was 1 : 2100 users with a fatality rate of 1 : 31 000. Serious hepatic disorders occurred in 1 : 11 1000 pyrimethamine-sulphadoxine prescriptions, 1 : 75 200 pyrimethamine-dapsone prescriptions, and in 1 : 15 650 amodiaquine users. 35% of cases received these drugs needlessly as they were not exposed to drug resistant strains of *Plasmodium falciparum*. Since few serious reactions have been reported to chloroquine plus proguanil, these data support guidelines which restrict the use of reviewed drugs for those at greatest risk of infection. Dosage data indicated that fatalities had taken higher doses and continued prophylaxis after onset of symptoms. Two thirds of serious reactions to the compound antimalarials were reported in females.

Introduction

The increased exposure of non-immune travellers to chloroquine resistant strains of *Plasmodium falciparum* has necessitated the prescription of alternative antimalarial drugs to which these strains are sensitive. Pyrimethamine-sulphadoxine (PS), pyrimethamine-dapsone (PD) and amodiaquine have, however, all been associated with serious adverse reactions in users and published reports have had substantial impact on malaria prophylaxis recommendations. Data procured from retrospective studies in the United States[1], Sweden[2,3] and one locality in Britain[4] have provided best estimates of the expected rate of some reactions in users. Quantitative analysis balancing the relative risk of toxicity against risk of malaria has also been comprehensively described[5]. Internationally, estimates of rates of serious cutaneous reactions to PS have varied substantially; ranging from 1 : 150 000 users in Switzerland[6], 1 : 10 000 users in Sweden[2], to between 1 : 5000 and 1 : 8000 users in the United States[1]. However, calculation of users were derived from different sources and methodologies. Reported rates of serious reactions in British users have not been measured. In order to clarify the risk of toxicity in Britain, cases with serious reactions to PS, PD and to amodiaquine were investigated retrospectively. Multiple denominator sources were investigated to determine their influence on rate analysis.

Methods

Chemoprophylactic drugs sold in Britain

The number of British travellers prescribed PS, PD and amodiaquine was estimated from data collated by the Prescription Pricing Authority (PPA) and the Department of Health (DOH). These data were based on a 1 : 200 random sample of prescriptions in England and Wales and a 1 : 100 random sample in Scotland and provided information on the number of prescriptions issued in Britain each year and the average number of tablets prescribed per individual. Data exclude private and hospital prescriptions. In tandem with this, we requested drug sales data from the relevant pharmaceutical companies to investigate whether these corresponded with DOH prescriptions. Pharmaceutical data, derived from their ex-factory sales, were estimates of the total number of tablets sold in Britain each year, but not the number of prescriptions. Since amodiaquine could be bought over the counter in British pharmacies without a prescription, denominators for this drug were based on pharmaceutical sales data rather than prescriptions. The average number of British users was based on the number of packs of 100 tablets sold in Britain annually, and assumed that British residents using amodiaquine did so for a mean of 10 weeks[8].

National reports of adverse drug reactions

The Committee on Safety of Medicines (CSM) runs a national postmarketing surveillance system for the collection of spontaneously reported adverse drug reactions in Britain (the yellow card reporting scheme[7]). Clinicians have been encouraged to report all suspected reactions to new drugs including minor reactions. Reporting of serious reactions, defined as fatal, life-threatening, disabling or incapacitating, has been requested for established drugs. Yellow card data are compiled to portray all reports and serious reactions. Drug culpability and seriousness are judged by a physician at the CSM. All reported adverse

0141-0768/90/
020082-04/$02.00/0

reactions suspected as caused by PS, PD and amodiaquine were investigated. Personal identifiers on CSM reports were used to cross-check data against respective reports of reactions that were published in the medical literature.

Rate analysis

Rates of all serious reactions and principal reactions were estimated for each drug. The principal presenting reaction for each case was used for rate analysis. The poisson distribution was used to calculate 95% confidence limits of the rates.

Results

Case reports attributed to pyrimethamine-sulphadoxine

A total of 41 cases with reactions associated with PS have been reported since 1980. Of these, 21 (51%) satisfied the CSM definition of a serious adverse reaction. Eight cases had serious cutaneous reactions recorded as a serious reaction; six were diagnosed with Stevens-Johnson syndrome. All four fatalities were associated with serious adverse cutaneous reactions, with a case fatality rate of 50%. Four cases (one of whom also presented with a serious cutaneous reaction) had hepatitis or abnormal hepatic reactions. Three presented with blood cell dyscrasias; with agranulocytosis, granulocytopaenia and thrombocytopaenia. Two cases had serious reactions affecting the eyes; toxic amblyopia and iritis. The other four cases with serious reactions to PS had bronchospasm, spontaneous abortion, precordal chestpain and convulsions, respectively. Two thirds of the cases were females. The mean age of all cases was 38 years (range 5-64 years). Ages of fatal cases ranged from 5 to 64 years. A mean of 3 tablets of PS were taken prior to onset of symptoms, ranging from 1 to 8 tablets with a median of 2 tablets. The mean total dose taken by patients with cutaneous reactions was 3.4 tablets (range 1-6); with a mean of 3.8 (range 2-6) in fatalities and 2.3 (range 1-6) in survivors. Tablets were taken for a mean of 2.5 weeks prior to onset of all serious reactions (range 1-8). This was lower for cutaneous reactions with a mean of 1.6 weeks (range one to three). Five (55%) of the nine cases had concomitantly taken chloroquine.

Case reports attributed to pyrimethamine-dapsone

Between 1972 and mid-1988, 76 reported reactions were attributed to PD. Of these, 40 (53%) were classified as serious. Fifteen patients had serious blood cell dyscrasias, recorded as agranulocytosis, granulocytopaenia or leucopaenia. Five fatalities were associated with blood cell disorders giving a case fatality rate of 33%. The sixth death occurred in a case with myocarditis. Three cases were reported with cyanosis associated with methaemoglobinaemia. Six patients were diagnosed with respiratory disorders; three with pulmonary eosinophilia, two with influenza-like syndrome and one with dyspnoea. Skin disorders were the principal symptom in four patients; with epidermal necrolysis, angioedema and bullous eruptions. Four cases were diagnosed with hepatic disorders. Three women using PD delivered malformed babies; one of these was known to be stillborn. However, dates of their last menstrual period and their exposure to drugs were not recorded; there was thus no certainty that the malformations were associated with exposure to drugs during the first trimester. Convulsions, exacerbated epilepsy, pancreatitis and a generalized allergic reaction were reported in four cases, respectively.

Two thirds of cases were females. The mean age of cases was 42 years (range 10-77 years); in cases with white blood cell dyscrasias the mean age was 50 years (range 18-77 years). Four of the five fatalities with these reactions were over 50 years of age. A mean of 4 tablets were taken prior to onset of all serious reactions (range 1-14) with a median of 3 tablets. The mean total dose taken by patients with blood dyscrasias was 9.1 tablets (range 6 to 18). Fatalities had taken between 16 and 18 tablets compared with a mean of 6.5 tablets (range 1-6) in survivors. Eight patients with blood dyscrasias had taken one or less tablets a week (two used 1 tablet fortnightly). One taking PD once weekly died. Only three cases were known to have taken 2 tablets weekly, two of whom died. Tablets were taken for a mean of 3.9 weeks prior to onset of all serious reactions (range 1-9) and 6.6 weeks (range 5-8) in cases with white cell dyscrasias.

Case reports attributed to amodiaquine

Twenty-two cases of adverse reactions with two deaths associated with amodiaquine, were reported as

Table 1. Reported rates of serious adverse drug reactions (ADR) associated with pyrimethamine-sulphadoxine in Britain

	ADR cases		*DOH prescription data*			*Rates (95% CL§) (by prescription)*			
*Year**	*All*	*Deaths*	*Tablet sales†*	*Mean tablets per script*	*Prescriptions*	*All*		*Deaths*	
1980	2	1	9.0	22.5	0.4	200	(100-1650)	400	(70-15 800)
1981	—	—	41.0	25.6	1.6	—		—	
1982	1	—	74.6	15.6	4.8	4800	(900-189 700)	—	
1983	3	—	184.7	18.3	10.1	3400	(1150-15 300)	—	
1984	4	1	218.0	17.2	12.7	3200	(1200-11 650)	12 700	(2300-502 000)
1985	11	2	153.1	14.0	10.9	1000	(550-2000)	5 450	(1200-17 600)
1986	—	—	23.7	12.5	1.9	—		—	
1987	—	—	26.0	13.0	2.0	—		—	
All ADRs	21	4	730.1	16.4	44.4	2100	(1400-3400)	11 100	(4300-40 700)
Cutaneous ADRs‡	9	4	730.1	16.4	44.4	4900	(2600-10 800)	11 100	(4300-40 700)

*Year of reaction used but if unknown, date of report used

†Sales of tablets estimated by DOH based on their analyses of PPA prescriptions, in thousands

‡ADR cases with Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme

§95% confidence limits, poisson distribution

Table 2. Reported rates of serious adverse drug reactions (ADR) associated with pyrimethamine-dapsone in Britain

	ADR cases		DOH prescription data			Rates (95% CL[§]) (by prescription)			
Year*	All	Deaths	Tablet sales[†]	Mean tablets per script	Prescriptions	All		Deaths	
1979	—	—	245.7	26.4	9.3	—		—	
1980	1	—	458.9	24.3	18.9	18 900	(3400-747 000)	—	
1981	5	—	666.7	26.4	30.2	6000	(2600-18 600)	—	
1982	3	1	769.5	17.8	43.3	14 400	(4900-70 000)	43 300	(7800-1 711 500)
1983	10	3	810.5	19.3	42.1	4200	(2300-8800)	14 000	(4800-68 000)
1984	5	1	992.2	21.6	42.6	8500	(3650-26 200)	42 600	(7600-1 683 800)
1985	4	—	827.5	18.1	45.7	11 400	(4500-42 000)	—	
1986	2	—	606.2	17.2	35.3	17 650	(4900-145 700)	—	
1987	3	—	611.3	18.3	33.4	11 100	(3800-54 000)	—	
All ADRs	33	5	5918.5	19.9	300.8	9100	(6500-13 200)	60 200	(25 800-185 300)
Blood dyscrasias[‡]	15	4	5918.5	19.9	300.8	20 000	(12 200-35 800)	75 200	(29 400-276 000)

*Year of reaction used but if unknown, date of report used
[†]Sales of tablets estimated by DOH based on their analyses of PPA prescriptions, in thousands
[‡]ADR cases with granulocytosis, agranulocytosis, leucopenia
[§]95% confidence limits, poisson distribution

Table 3. Reported rates of serious adverse drug reactions (ADR) associated with amodiaquine in Britain

	ADR cases		Pharmaceutical data			Rates (95% CL[§]) (by user)			
Year*	All	Deaths	Tablet sales[†]	Mean tablets per user	Users[‡]	All		Deaths	
1985	9	1	365.5	20	18.3	2000	(1100-4400)	18 300	(3300-723 300)
1986	9	1	259.3	20	13.0	1400	(800-3200)	13 000	(2300-513 800)
All ADRs	18	2	624.8	20	31.3	1700	(1100-2900)	15 650	(4300-129 200)
Blood dyscrasias[‡]	14	1	624.8	20	31.3	2200	(1300-4100)	31 300	(5600-1 237 200)

*Year of reaction used but if unknown, date of report used
[†]Packs from pharmaceutical data, users calculated given mean of 4 weeks travel to malarious countries
[‡]ADR cases with granulocytopaenia or agranuloctyosis
[§]95% confidence limits, poisson distribution

clustered cases to the CSM between December 1984 and 1986. Of these, 19 were judged to be serious reactions to amodiaquine, of whom nine were reported in 1985 and nine in 1986. Seventeen cases were diagnosed with blood dyscrasias. There were 15 reports of agranulocytosis or granulocytopaenia, one with aplastic anaemia and one other with thrombocytopenia. The two fatalities had agranuloctyosis and aplastic anaemia. Two patients suffered hepatic disorders. Eleven (58%) of cases were males. The mean age was 43 years (range 18-71 years). One male of 18 years and a female of 62 years died. A mean dose of 2.8 g was taken prior to onset of all serious reactions (range 0.8-4.8 g) with a median of 2.8 g. The mean total dose taken by patients with white blood cell dyscrasias was 3.2 g (range 1.2-7.6 g). Tablets were taken for a mean of 6.9 weeks (range 1-12 weeks) prior to onset of all serious reactions and for 7.3 weeks (range 3-12 weeks) white cell dyscrasias alone. Fourteen (74%) cases also took proguanil.

Reported rates of serious adverse drug reactions

The mean reported rate of serious reactions to PS was 1 : 2100 prescriptions and for serious cutaneous reactions was 1 : 4900 prescriptions with a fatality rate of 1 : 11 100 (Table 1). Rates derived from denominators from the pharmaceutical company were 3.7 lower than estimates based on prescription data. Reporting rates for all serious reactions to PD were 1 : 9100 prescriptions, with a fatality rate of 1 : 60 200 (Table 2). Rates were not highest during the period when 2 tablets weekly were recommended, suggesting that reporting of reactions was delayed. The mean reported rate of white blood cell dyscrasias was 1 : 20 000 prescriptions. The reported rate of serious reactions to amodiaquine, based on over the counter sales data was 1 : 1700 users with a fatality rate of 1 : 15 560 (Table 3). The rate for serious white blood cell dyscrasias was 1 : 2200 users with a fatality rate of 1 : 31 300. Serious hepatic disorders occurred in 1 : 11 100 PS prescriptions, 1 : 75 200 PD prescriptions and in 1 : 15650 amodiaquine users.

Discussion

Reporting rates presented are crude indicators of the risk of toxicity from antimalarial drugs. Rates may have been over-estimated because denominators derived from prescriptions exclude private prescriptions. However, this may be offset by under-reporting of cases. Rates of serious cutaneous reactions to PS concurred with those reported in US and Swedish travellers, but was substantially higher than Swiss estimates. During this review, we identified that denominators derived from pharmaceutical companies included unsold drugs in pharmacy stores and sales destined for use abroad, bought in bulk by large companies and non nationals. Low rates in Switzerland may be associated with the inclusion of overseas sales data in their denominator. Our data illustrated annual variation in the reporting of cases and reaction rates. Temporal trends in reporting rates and types of reactions were particularly evident for PD; rates of serious blood cell dyscrasias were 10-fold lower between 1985 and 1987 than that of the previous 3 years. Clinicians are urged to continue reporting all serious reactions, including familiar and well publicised reactions.

Decision analysis has been encouraged as a tool for judging which drug to prescribe against drug resistant *P. falciparum* infections[5]. Rates presented here have been limited to reactions classified as serious by the CSM. The wide 95% confidence limits calculated illustrate that rate analyses, for relatively rare events, lacks precision. Importantly, between 10% and 20% of these cases were fatal, indicating the seriousness of reactions so described. Even when taking the many reporting biases into account, these data strongly suggest that the toxicity of these drugs is not uniform; the toxicity of amodiaquine appeared to be 5-fold higher than single weekly doses of PD. All levels of toxicity are excessive when compared with the combination of chloroquine plus proguanil. Few serious reactions have been reported to this regimen. Furthermore, potentially toxic drugs have also been misused; voluntary reporting of travel destinations indicated that 35% of cases had not visited areas with drug resistant strains of *P. falciparum*. Despite the spread of chloroquine resistance, chloroquine plus proguanil remains the regimen of choice and potentially toxic drugs are reserved for those exposed to multidrug resistant strains. Assistance with current malaria recommendations may be obtained by telephoning the Malaria Reference Laboratory (01 636 7921) or the Liverpool School (051 708 9393).

Acknowledgments: The views represented in this paper are those of the authors. We would like to thank the CSM for the use of their data and are grateful to the DOH and PPA for allowing access to, and publication of, their prescription data. Roche Products Ltd, The Wellcome Foundation Ltd, and Parke-Davis Research Laboratories are acknowledged for their helpful cooperation. Dr Ronald Mann, Dr Lars Rombo and Dr Kent Campbell are thanked for their constructive comments on the manuscript. The Leverhulme Trust and the Malaria Action Programme, WHO are thanked for their financial support during this study.

References

1 Miller KD, Lobel HO, Satriale RF, *et al.* Severe cutaneous reactions among American travellers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986;**35**:451-8
2 Hellgren U, Rombo L, Berg B, Carlson J, Wiholm B-E. Adverse reactions in sulphadoxide-pyrimethamine in Swedish travellers: implications for prophylaxis. *Br Med J* 1987;**295**:365-6
3 Friman G, Nystrom-Rosander C, Jonsell G, *et al.* Agranulocytosis associated with malaria prophylaxis with Maloprim. *Br Med J* 1983;**286**:1244-5
4 Hatton CSR, Peto TEA, Bunch C, *et al.* Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet* 1986;i:411-13
5 Peto TEA, Gilks CF. Strategies for the prevention of malaria in travellers: comparison of drug regimens by means of risk benefit analysis. *Lancet* 1986;i:1256-60
6 Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine-pyrimethamine in Switzerland. *Lancet* 1986;i:610
7 Mann R, ed. *Adverse drug reactions, the scale and nature of the problem and the way forward.* Parthenon 1987
8 Phillips-Howard PA. *The epidemiology of malaria in Britain.* PhD Thesis. University of London, 1988

(Accepted 31 October 1989. Correspondence to Dr P A Phillips-Howard, Malaria Action Programme, World Health Organization, 1211 Geneva 27, Switzerland)