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REVIEW ARTICLE

Hypersensitivity Reactions to Dapsone: A Systematic Review

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Dapsone is widely used in the treatment of leprosy and several chronic inflammatory dermatological conditions. Hypersensitivity reactions to dapsone are potentially fatal adverse drug reactions with unknown prevalence and risk factors. We performed a systematic review covering all reported cases of hypersensitivity reactions, in order to systematically summarize the published evidence on prevalence, clinical course and fatality rate. Articles were identified through standardized search strategies. Included studies were reviewed for hypersensitivity characteristics and odds ratios were calculated in univariate and multivariate regression models to assess the risk factors for fatal outcome. A total of 114 articles (17 epidemiological studies, 97 case reports) totalling 336 patients with hypersensitivity reactions were included for analysis. From the epidemiological studies a total hypersensitivity reaction prevalence rate of 1.4% (95% confidence interval 1.2–1.7%) was determined. Mucosal involvement, hepatitis, higher age and disease occurrence in non-affluent countries were associated with higher risk of fatal outcome. Overall, the fatality rate was 9.9%. ***Key words: dapsone; adverse drug reaction (drug safety); drug hypersensitivity; systematic review; death rate; epidemiological studies.***

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The sulphone dapsone (4,4-diaminodiphenylsulphone) (1) has been used as an oral drug since 1949 (2). Initially, it was approved for leprosy, for which it is still frequently used.

In addition to its antimicrobial effects dapsone is a potent anti-inflammatory agent with high effectiveness in dermatitis herpetiformis and a wide variety of other inflammatory dermatological conditions (3, 4). Although dapsone is generally well tolerated and suitable for long-term treatment, adverse drug reactions (ADR) may occur (5). Obligatory (dose-dependent) ADRs include haemolytic anaemia and methaemoglobinaemia (6). Important, less well-known, potentially fatal ADRs with unknown pathomechanisms are hypersensitivity reactions (HR) to dapsone, such as the so-called dapsone syndrome (synonymous with sulphone syndrome) (11).

First mentioned in 1951 (7) (after Lowe & Smith referred to dapsone syndrome as "glandular fever" in 1949 (8)) it is generally described as a combination of at least two of the following four symptoms: (*i*) fever, (*ii*) lymphadenopathy, (*iii*) generalized rash, and (*iv*) hepatitis occurring after dapsone intake (9). The complete syndrome consists of all four of these symptoms (10). Its occurrence rate is subject to controversial assumptions, with estimates ranging from 2% to 12% (12). Based on individual observations, the fatality rate is assumed to be approximately 13–15% (13–15). To date, systematic research concerning the most important clinical, epidemiological, and prognostic features of HR to dapsone, is missing. We performed a systematic review covering all reported cases of HR in order to summarize the evidence on the frequency of HR occurrence as well as the clinical presentation, risk factors and fatality rate.

METHODS

Literature search

A standardized literature search was conducted of all published epidemiological studies and case reports of HR to dapsone using the online databases Medline (via PubMed), CINAHL (via EBSCO Host) and ISI Web of Science, each from inception until October 2009. Search terms were "[sulphone OR sulfone OR dapsone OR diaminodiphenylsulfone OR diaphenylsulfone] AND [syndrome OR hypersensitivity]". A total of 444 potentially relevant articles were found. In addition, Scopus and Google, as well as the reference lists of all identified articles were searched manually by the first author (ML), identifying 19 and 29 additional relevant papers, respectively. No publication language restrictions were imposed. All journal articles or article abstracts of HR to dapsone, including severe forms, such as drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) (16, 17), were included, and less severe forms (presence of at least two of the four symptoms fever, lymphadenopathy, generalized rash and hepatitis), which provided original data and were published between January 1951 and October 2009. A total of 492 articles was screened for eligibility, 114 of which were included in this systematic review (Fig. 1).

Data extraction

Data extraction comprised information about study design, patient characteristics, clinical and paraclinical characteristics of HR, as well as therapy and outcome (full recovery vs. death). A 10% random sample of the included articles was randomly chosen and then abstracted independently by a second investigator (JS). Resulting

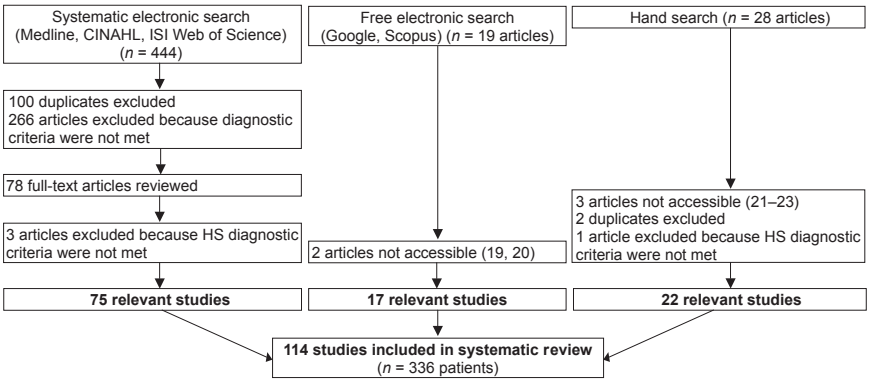

Fig. 1. Identification of relevant studies for inclusion in the systematic review.

agreement between the two reviewers was 99.3%. Disagreements between the reviewers were resolved by discussion.

Data synthesis and statistical methods

The descriptive content of the publications was studied and merged, and the associations between variables analysed, with a focus on the patient's outcome (recovery vs. death). For the analyses relating to countries, we defined two strata using the World Bank criteria regarding income. "High-income countries", with a gross national per-capita income (GNI) of at least US $11,906 in 2008, were classified as affluent countries, and the remaining countries were referred to as non-affluent countries (18). Information on age of patients and latency between dapsone initiation and HR onset is presented by weighted means (weighted by number of patients) to consider information from epidemiological studies. For further evaluation patient's age was transformed to two categories with the median as cut-off. Reported skin symptoms were classified in the following three groups: (*i*) exanthema and erythema, (*ii*) erythroderma, and (*iii*) rash (not specified). When dapsone 100 mg/day was given only once a week (for malaria prophylaxis), it was listed as 14.3 mg/day.

To estimate the risk for fatal outcome odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. A multivariate logistic regression model was used to analyse the relationship between sociodemographic factors (sex, age, affluence), disease characteristics (dapsone indication and administration terms, latency between dapsone initiation and HR onset, clinical manifestations), and characteristics related to the medical system (HR therapy) and the final outcome of the HR to dapsone (recovery vs. death). For this analysis only patients with a biunique parameter combination ($n=203$) could be included. Interaction analyses were also performed on these parameters. Negative and missing information were always differentiated, leading to differing values for missing data in the single analyses. All analyses were carried out at the individual patient level using SPSS version 17.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Results of literature search

A total of 114 studies, comprising 336 patients with HR to dapsone, met the inclusion criteria and were analysed (Fig. 1). Case reports held the majority of the studies ($n=97$) (10, 24–120) and reported on 120 patients, whereas 17 included articles were observational epidemiological studies (16 retrospective cohort studies, one prospective cohort study) (7, 9, 121–135) reporting on 216 patients.

Characteristics of the study and the patients

A total of 92 articles were published in English, 6 in Spanish (31, 52, 74, 88, 101, 105), 5 in French (41, 57, 64, 67, 128), 4 in Portuguese (63, 81, 84, 97), 3 in Korean (70, 87, 103) and 2 in each of Japanese (48, 83) and Chinese (109, 133).

A total of 118 (40.8% of 289) patients were female. Of the 265 reported patients with HR to dapsone, the weighted mean age was 35.2 years (age range 5–83 years). In epidemiological studies information on the total dapsone user population regarding gender and age, however, was given only in exceptional cases. The majority of HR publications (63 of 114), and thus patients with HR, originated from Asian countries (72.6% of 336). Ninety-three patients (27.7% of 336) came from affluent category countries.

Chronic inflammatory dermatoses, e.g. dermatitis herpetiformis Duhring, acne and lupus erythematosus, totalled 17.2% of the reported dapsone indications ($n=302$). Furthermore, non-infectious entities comprised mainly vasculitides and arteritides (3.3% of 302). However, with 71.9% (217 of 302) leprosy was the most prevalent indication for dapsone use. Malaria prophylaxis, *Pneumocystis jiroveci* pneumonia in HIV patients, and tuberculosis were present as other infectious conditions (7.6% of 302).

As multidrug therapy (MDT) is the recommended regimen for leprosy treatment (138) the percentage of co-medication in dapsone users was very high (68.5% of 302). MDT consists of dapsone and rifampicin for paucibacillary (PB) leprosy and additional clofazimine in multibacillary (MB) leprosy. Further co-medications were mostly antibiotics, glucocorticosteroids and pyrimethamine. In most cases dapsone dosage was 100 mg/day (81.7% of 263).

In epidemiological studies, there was no difference regarding indications, dapsone dosage and co-medication between total of dapsone users and patients developing HR (Table SI, available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1268). Almost all cohort studies (87.5%) were carried out on leprosy patients (7, 9, 121–134). From the information

on total numbers of dapsone users given in epidemiological studies HR prevalences were determined, leading to a total prevalence rate of 1.4% (95% CI 1.2–1.7%; range 0.2–24.3%) (121, 123).

Characteristics of hypersensitivity reactions

Weighted mean of latency between dapsone initiation and occurrence of first hypersensitivity symptoms was 28.0 days (range 6 h to 21 weeks; $n=166$). Fever and skin symptoms were the most prevalent HR (96.6% of 291 and 92.0% of 300). Of the 130 patients with information on presence/absence of mucosal involvement 44.6% were affected. Hepatitis and lymphadenopathy were reported in 81.9% of 298 and 73.7% of 270 patients, respectively. All 4 symptoms were presented by 61.6% of the 250 reported patients. Concomitant symptoms, such as nausea and vomiting, were reported in 165 patients. Eosinophilia was seen in 45.4% of 183 patients and leucocytosis in 58.5% of 142 patients.

Regarding therapy of HR, cessation of dapsone was carried out in all reported cases ($n=251$). Forty-eight patients continued to take dapsone after HR onset (median time 7 days; $P_{25}=5$ days; $P_{75}=10$ days; $n=37$). Systemic glucocorticosteroid treatment was administered in 82.1% of patients (170 of 207), mostly in dosages of 0.8–2.0 mg/kg body weight of (methyl-) prednisolone. Further reported procedures ranged from supportive care, such as topical treatment of the rash ($n=16$) or systemic administration of antibiotics ($n=40$) and antihistamines ($n=20$), to intensive care.

Recovery periods ranged from 6 days to several months ($n=72$; weighted mean 26.7 days) (89, 101). With 33 deceased hypersensitivity patients lethality was 9.9%. Patients deceased 5–60 days (mean 20.1 days; $n=14$) after the onset of first hypersensitivity symptoms (63, 123). Liver failure was the most frequent cause of death ($n=18$) (9, 24, 26, 42, 49, 61, 121, 122, 127, 132–134). Other causes of death were sepsis/shock ($n=4$) (30, 39), lung failure ($n=4$) (106, 123, 134), multi-organ failure including liver failure ($n=1$) (72), bone marrow failure ($n=2$) (9, 62), and myocardial infarction ($n=1$) (125). In 3 patients the cause of death was not specified (two of them discharged themselves and died at home) (123).

Risk factors

Table I summarizes patient characteristics stratified by outcome of HR (recovery vs. death).

In bivariate analyses mucosal involvement (OR 10.96; 95% CI 1.31–91.99; $p=0.03$; $n=135$), hepatitis (OR 8.20; 95% CI 1.10–61.39; $p=0.04$; $n=295$) and affluence of countries (OR 6.72; 95% CI 1.57–28.66; $p=0.01$; $n=334$) were significant risk factors for fatal outcome of HR to dapsone (Table II). Delayed drug cessation showed a non-significant tendency to increase risk for fatal outcome (OR 1.88; 95% CI 0.28–6.15; $p=0.30$; $n=251$). In summary statistics also, rash appeared to be a significant risk factor ($p=0.04$) (Table I). However, as all deceased patients had skin symptoms, regression could not be applied.

Results of the multivariate analysis are summarized in Table II. The multivariate logistic regression model revealed a significant association between age (OR 2.95; 95% CI 1.07–8.11; $p=0.04$; $n=164$) and leprosy as dapsone indication (OR 5.14; 95% CI 1.09–24.27; $p=0.04$; $n=162$) (Table II).

Interaction analyses did not show any evidence for effect modification by age, sex or affluence.

DISCUSSION

Statement of main findings

Based on the published epidemiological studies, the prevalence of HR to dapsone is 1.4% (95% CI 1.2–1.7%). Overall, the case-fatality rate is 9.9%. Mucosal involvement, rash, hepatitis, higher age, leprosy as indication for dapsone use, and disease occurrence in non-affluent countries were associated with a higher risk of fatal outcome. However, the association between higher age and fatal outcome of HR to dapsone did not reach statistical significance in all analyses. Frequency of HR onset may be influenced by the general and immunological status of leprosy patients (132). It is worth noting that the association with leprosy treatment may largely be accounted for by higher incidence rates of leprosy in non-affluent countries. Mucosal involvement could be shown to be a potent risk factor for fatal outcome of HR to dapsone. Rash was also associated with a higher risk of fatal outcome in the published reports. However, diagnostic criteria for rash were not declared, although rash may refer to an acute reddening rather than exanthema. It is possible that more acute clinical courses may account for a higher risk of fatal outcome. Further research is necessary to clarify this important issue.

Severity of skin symptoms and severity of internal organ involvement may not correlate (108). Besides the liver, other internal organ involvement, such as renal (100), cardiac (120), pulmonary (108) or pancreatic (77), were present as additional complications. Our systematic review suggests the need to discontinue dapsone treatment immediately in case of suspected dapsone hypersensitivity, as delayed drug cessation appears to double the risk for fatal out-come. Latency of HR onset ranged from 6 h (126) to 21 weeks (57), but in general it ranged from 3 to 5 weeks.

As multi-drug therapy is used in leprosy, interactions between the different anti-leprosy drugs may influence the likelihood of HR occurrence (136). Rifampicin is known to induce dapsone metabolism (137). In our analyses co-medications and dapsone dosage do not seem to affect the occurrence or outcome of HR to dapsone.

Table I. *Sample characteristics stratified by outcome (recovery vs. death)*

	Total ($n=334$)			Recovery		Death		
Characteristic	*n*	%	NR	*n*	%	*n*	%	*p*-value
Female sex	110	39.7	57	104	41.3	6	24.0	0.09
Age, years, median ($P_{25;}P_{75}$)	27 (20;45)		169	26 (19;45)		35 (24;53)		0.09
Continent			0					0.005
Asia	242	72.5		217	72.1	25	75.8	
Europe	42	12.3		42	14.0	0	0	
North America	12	3.6		11	3.7	1	3.0	
South America	12	3.6		11	3.7	1	3.0	
Australia, Oceania	13	3.9		8	2.7	5	15.2	
Africa	13	3.9		12	4.0	1	3.0	
Affluent-country treatment[a]	93	27.8	0	91	30.2	2	6.1	0.003
Type of indication			36					0.17
Chronic inflammatory diseases	51	17.1		49	18.4	2	6.3	
Leprosy	214	71.8		186	69.9	30	87.5	
Other infectious entities	23	7.7		21	7.9	2	6.3	
Other non-infectious entities	10	3.4		10	3.4	0	0	
Dapsone dose			73					0.18
<100 mg/day	23	7.9		22	9.3	1	4.2	
100 mg/day	213	81.6		191	80.6	22	91.7	
>100 mg/day	25	9.5		24	10.1	1	4.2	
Co-medication	203	68.1	36	183	67.8	20	71.4	0.69
Latency			171					0.14
≤20 days	40	24.5		39	26.7	1	5.9	
21≤28 days	57	35.0		49	33.6	8	47.1	
29≤35 days	34	20.9		31	21.2	3	17.6	
≥36 days	32	19.6		27	18.5	5	29.4	
Complete HR[b]	149	61.1	90	137	59.8	12	80	0.12
Fever	277	96.9	48	250	96.9	27	96.4	0.89
Lymphadenopathy	196	73.7	68	181	73.0	15	83.3	0.34
Hepatitis	239	81.0	39	208	79.4	31	96.9	0.015
Skin symptoms	274	91.9	36	245	90.9	33	100	0.07
Exanthema/erythema	155	57.4		141	58.5	14	48.3	0.22
Erythroderma	36	13.3		35	14.5	1	3.4	>0.99
Rash	79	29.3		65	27.0	14	48.3	0.04
Mucosal involvement	53	42.1	208	46	39.0	7	87.5	0.01
Concomitant symptoms	149	89.2	167	136	88.3	13	100	0.37
Leukocytosis	77	56.6	198	72	56.3	5	62.5	>0.99
Anaemia	102	55.7	153	96	54.9	6	75.0	0.31
Eosinophilia	78	43.8	156	74	43.3	4	57.1	0.70
Dapsone cessation			83					0.56
Immediately after HR onset	85	33.9		79	34.8	6	25.0	
Delayed to HR onset	48	19.1		42	18.5	6	25.0	
Time point unspecified	118	47.0		106	46.7	12	50.0	
Systemic glucocorticosteroid therapy	167	82.3	131	155	82.0	12	85.7	>0.99

[a]Based on gross national income per capita. [b]Presence of all 4 cardinal symptoms. NR: not reported; HR: hypersensitivity reactions.

Regarding the metabolism of dapsone, two main pathways are known: acetylation and hydroxylation, with dapsone hydroxylamine being thought to be responsible for side-effects (138). The exact underlying pathomechanisms, however, are unclear (11, 127).

Although no double-blind studies on efficacy of oral glucocorticosteroids exist, anecdotal positive experience led to common use of oral glucocorticosteroids in the treatment of HR to dapsone (108, 132). Systemic glucocorticosteroids were administered in 82.1% of reported cases ($n=207$). However, glucocorticosteroids are recommended only in patients with internal organ involvement (139). Our review suggests that systemic steroids should also be considered in cases of HR with mucosal involvement in the absence of organ involvement, but still more clinical evidence is needed to strengthen this suggestion. If used, glucocorticosteroids should be tapered gradually over one month, as dapsone persists up to 35 days in organs due to protein binding (73).

Of the 33 deceased patients, liver failure was the most frequent cause of death ($n=18$) and one patient died of multi-organ failure including liver failure. Other reasons for death were mostly described as further adverse drug reactions to dapsone in the context of HR (sepsis/shock, lung failure, bone marrow failure ($n=10$)).

Strengths and limitations of the review

This study meets the standards for systematic reviews and is based on the highest available number of patients showing HR due to dapsone. Multiple search strategies accounted for minimizing language and publication bias.

Table II. *Logistic regression on outcome (reference = recovery) univariate and multivariate (full version (Table SII) available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1268)*

	Bivariate analysis $n=334$ (unadjusted)			Multivariate analysis $n=203$ (adjusted to gender and age)		
Characteristic (reference)	OR (95% CI)	*p*-value	NR	OR (95% CI)	*p*-value	NR
Age (≥28 vs. ≤27 years)	2.29 (0.88–6.01)	0.09	167	2.95 (1.07–8.11)	0.04	39
GNI affluence (affluent)	6.72 (1.57–28.66)	0.01	0	4.11 (1.13–14.99)	0.03	39
Type of indication (chronic inflammatory dermatoses)			36			41
Leprosy	3.69 (0.85–16.02)	0.08		5.14 (1.09–24.27)	0.04	
Other infectious entities	2.33 (0.31–17.69)	0.41		2.38 (0.30–19.16)	0.41	
Other non-infectious entities	Ø[a]	NC		Ø[a]	NC	
Latency (≤20 days)			171			47
21–28 days	6.37 (0.76–53.10)	0.08		4.95 (0.56–43.49)	0.15	
29–35 days	3.77 (0.37–38.09)	0.33		3.60 (0.35–37.49)	0.28	
≥36 days	7.22 (0.80–65.34)	0.06		7.64 (0.80–72.84)	0.077	
Hepatitis (absent)	8.20 (1.10–61.39)	0.04	39	3.12 (0.38–25.52)	0.29	50
Mucosal involvement (absent)	10.96 (1.31–91.99)	0.03	208	Ø[b]	NC	144

[a]None of these patients deceased. [b]All deceased patients with mucosal involvement dropped out from analysis. NR: not reported; NC: not calculable.

We used multiple adjusted logistic regression models to assess risk factors for fatal outcome of HR to dapsone.

One limitation of this review concerns the reporting quality and completeness of the included papers. In case reports, the information aimed to collect for this review was not reported completely in all publications. Therefore it is not possible to determine the incidence of HR due to dapsone based on currently available data, and thus we assessed prevalence instead. In epidemiological studies individual patient data were not provided, so a comparison between all dapsone users and HR patients could not be conducted.

Implications for future research

Genetic risk factors and gene-environment-interaction concerning the occurrence and outcome of HR to dapsone have not yet been investigated and are subject to future research.

Regarding prognostic factors, patient's age and clinical manifestations, such as mucosal involvement and hepatitis, are now identified, and in further studies with more appropriate data perhaps further prognostic factors, for example, dapsone intake duration, co-medication or ethnicity, could be specified.

Meaning of the study

Dapsone is effective in the treatment of leprosy, other infectious diseases, and a broad set of non-infectious dermatological conditions, e.g. dermatitis herpetiformis (6). Dapsone is frequently used worldwide and its use has been predicted to increase further, especially in non-leprosy conditions (135). Our review is highly relevant for clinical practice, as it indicates that HR to dapsone are not rare but occur in more than 1% of all cases. They are associated with a fatality rate of approximately 10% and, as there is no reliable test to predict the risk of dapsone hypersensitivity, the possibility of HR and its appearance should be explained to every patient receiving dapsone. In particular, in the first 3-month period of therapy, clinical and laboratory controls are very important, as more than 99% of HR cases after dapsone intake developed within this period.

Clinicians should be aware of HR to dapsone, as early recognition of HR, and prompt withdrawal and symptomatic treatment/minimal use of other drugs (132) are recommended to improve outcome.

Conflicts of interest. G.W. served as a paid lecturer for dapsone manufacturer Riemser in Germany.

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