

Delayed pressure urticaria – Dapsone heading for first-line therapy?

Sonja Alexandra Grundmann, Sabine Kiefer, Thomas Anton Luger, Randolph Brehler
Clinic and Polyclinic for Dermatological Diseases, Münster University Hospital, Germany

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Keywords

- dapsone
- urticaria
- chronic urticaria
- pressure urticaria
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Summary

Background: Pressure urticaria as a subform of physical urticaria is rare and treatment is often difficult. Established therapeutic regimes include antihistamines (generally exceeding approved dosages in order to achieve a therapeutic benefit) or antihistamines combined with montelukast. Complete relief of symptoms is difficult.

Patients and methods: We used dapsone as an early therapeutic alternative in the event of treatment failure and established a standardized therapeutic regime at our clinic. We surveyed 31 patients retrospectively who had received dapsone between 2003–2009.

Results: In 74 % of patients in whom symptoms persisted despite established therapies, the results of treatment with dapsone were good or very good. Longer-term pressure urticaria and the co-existence of a chronic spontaneous urticaria were associated with a smaller benefit ($p < 0.05$). No significant effects were found related to age, gender, duration of therapy, side-effects, or Met-Hb elevation (a tendency toward a decreased benefit was associated with middle-age, male sex, shorter duration of therapy, observed side-effects, and Met-Hb elevation).

Conclusions: Therapy is well tolerated and results in a good therapeutic benefit which lasts after termination of therapy. With adequate monitoring, the use of dapsone in patients with pressure urticaria has such a good risk-benefit ratio that we support early treatment initiation.

Introduction

Delayed pressure urticaria (DPU), a subtype of physical urticaria, is rare and treatment is difficult. Beyond pressure as a triggering factor, many patients also have chronic spontaneous urticaria (2–40 % of patients) [1–3]. Isolated pressure urticaria makes up <1 % of all forms of urticaria [4]. One main trigger is continued vertical application of pressure; after a latency period of 4–8 hours swelling appears at affected sites (especially on the shoulders, waist, palms of the hands, plantar surfaces of the feet, on the back and buttocks) [5]. Swelling may be accompanied by local pain, redness, excessive warmth, burning, and itching. Systemic symptoms such as fatigue, fever,

myalgia, arthralgia, and cephalgia, as well as an elevated erythrocyte sedimentation rate and leukocytosis have also been reported [4, 6]. Swelling persists for 8–48 hours. Diagnosis consists of taking a careful patient medical history, performing a standardized pressure challenge with several reading intervals (immediately, after 30 minutes and after 4, 6, 8, and 24 hours) [7]. Histological analysis shows inflammatory infiltrates that resemble an IgE-mediated late-phase reaction. Unlike other forms of urticaria, which are often triggered by infection, such factors are rarely the cause of pressure urticaria except in isolated case reports [8, 9]. Pressure urticaria is often chronic, lasting up to 6–9 years until spontaneous remis-

sion occurs [10]. Men are affected twice as often as women with a peak age incidence of about 30 years [11]. The disease causes considerable impairment of quality of life, especially considering that it is difficult to avoid application of vertical pressure. Known drug treatment schemes include antihistamines as monotherapy (first-line therapy, but with low efficacy), although the approved dosages must usually be exceeded for successful treatment, or combination use of antihistamines and montelukast [12, 13]. Therapy often fails to alleviate symptoms completely. Systemic steroids are often effective, but are not recommended for long-term use given the side effects associated with their prolonged use. The

Table 1: Dosage of dapsone therapy.

1 week	25 mg dapsone + 1 g vitamin C
2 weeks	50 mg dapsone + 1 g vitamin C
3 weeks	100 mg dapsone + 1 g vitamin C
> 4 weeks	150 mg dapsone + 1 g vitamin C

sulfone derivative dapsone (diaminodiphenyl sulfone) is considered to be only a fourth-line treatment option for chronic urticaria [9, 14], but it is increasingly considered a viable treatment option, especially for pressure urticaria. Although it is well known that dapsone, an inhibitor of folic acid synthesis, can neutralize oxygen free radicals and has inhibitory effects on leukotrienes and prostaglandin metabolism, the precise mechanism of action in the pathophysiology of pressure urticaria is not well understood [15]. Side effects of dapsone include dose-dependent hemolysis and methemoglobinemia. Glucose-6-phosphate dehydrogenase deficiency must be ruled out before beginning treatment. Other therapies that have been described include methotrexate, TNF- α blockers, and immunoglobulins [9, 16, 17]. The exact pathophysiological mechanisms of their effects in pressure urticaria are largely uncertain, however, and hence the development of tailored treatment regimens for this extremely difficult to treat disease is not yet foreseeable. There are also isolated reports on the effective use of the anti-IgE antibody (omalizumab) [18, 19].

Patients and methods

Between 2002 and 2009, 64 patients with pressure urticaria were treated at our clinic. The diagnosis of pressure urticaria was confirmed by medical history and standardized pressure challenge tests. All patients were examined according to current guidelines on the diagnosis and treatment of urticaria using clinical

and laboratory chemical tests, and in some cases imaging studies, for underlying systemic diseases. Treatment schemes were adopted based on the relevant guidelines. Level 1: low-dose antihistamines; level 2: high-dose antihistamines; and level 3: antihistamines plus montelukast.

Patients who previously had shown no response to established therapies were given dapsone according to the scheme presented in Table 1, following a negative result from a search for manifest causes of pressure urticaria. Dapsone was given in increasing dosages, beginning with 25 mg, along with vitamin C (Table 1) [15, 20]. All patients underwent screening for glucose-6-phosphate dehydrogenase deficiency as well as an initial blood differential and measurement of Met-Hb. During therapy, necessary check-ups were performed by the patient's family physician. During treatment, Met-Hb levels should not exceed 10 %. Patients were made aware of the off-label use of the drug. A retrospective descriptive data analysis of the treatment response to dapsone was performed and accompanying factors were recorded such as age, treatment duration, history of the disease, and side effects. Symptom improvement was recorded on an 11-point numeric scale (NRS-11). A score of 0–3 represented a very good treatment response, a score of 4–6 was considered a good response, and scores between 7–10 indicated a poor response to therapy (i.e., symptom improvement of less than 30 %). Success was defined as a very good or good treatment response.

Statistical analysis

The data were recorded in Microsoft® Excel (Version 2003, Microsoft, Redmond, WA, USA) tables and statistical analysis was performed using SPSS® (Version 17.0, SPSS Inc., Chicago, IL, USA). Statistical significance for nominal and ordinal categories was tested, depending on the group size, using Fisher's exact test or the Chi² test. A p-value <0.05 was considered statistically significant. The metric data were tested for normal distribution and equal variance and the t-test used to determine the significance of the differences (p<0.05).

Results

Out of 64 patients with pressure urticaria, 31 were given dapsone (treatment duration 9.7 ± 5.2 weeks). Compared with the remainder of patients, the patients had the same age distribution (p=0.038) and there were no significant differences in sex distribution (p=0.137, Table 2). Clinical severity of disease was similar for the two groups.

74 % of patients in whom established therapies failed to achieve complete healing had a very good or good response to dapsone (24 vs. 7 patients) (Figure 1). In 7 patients the symptoms resolved completely.

Among the patients who received dapsone 48 % were diagnosed with chronic spontaneous urticaria with additional pressure components (Table 3). The treatment response to dapsone was higher among patients without accompanying chronic spontaneous urticaria (14 out of 15 patients, 93 %, of whom 4 had complete relief of symptoms), while in patients with accompanying chronic spontaneous urticaria only 10 out of 16 patients (63 %) responded to treatment (p=0.05, Figures 2, 3 complete relief of symptoms).

Although age (p=0.881) and sex (p=0.652) had no significant influence on treatment success, there was a tendency toward a slightly less than average

Table 2: Demographic data of patients given antihistamines or dapsone (n.s.).

	dapsone			without dapsone		
	female	male	total	female	male	total
n	21 (68 %)	10 (32 %)	31 (100 %)	16 (49 %)	17 (51 %)	33 (100 %)
age/years	39 $\pm$ 10	46 $\pm$ 6	41 $\pm$ 9 (22–56)	46 $\pm$ 11	48 $\pm$ 17	47 $\pm$ 14 (23–83)

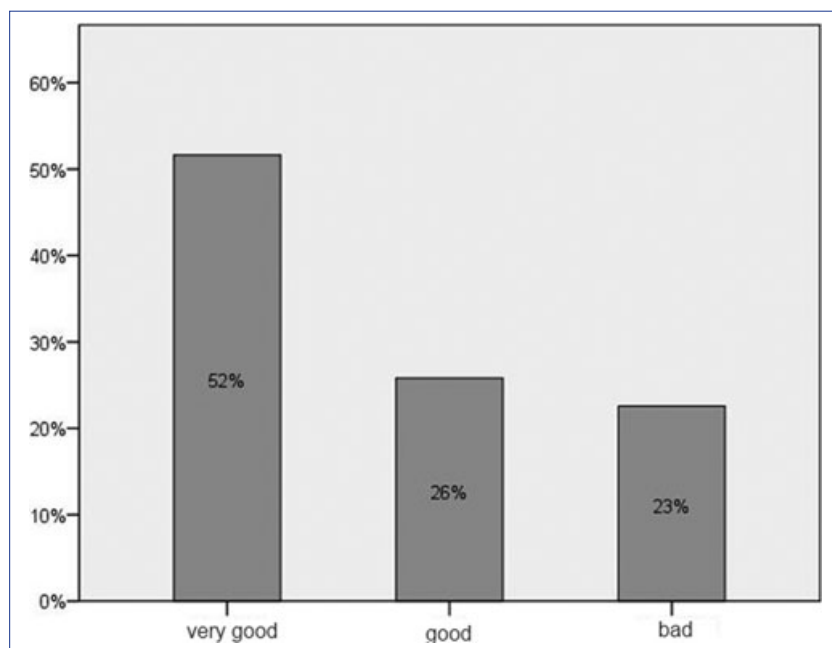


Figure 1: Benefit of treatment with dapsone (n=31).

Table 3: Benefit of dapsone therapy in patients with co-existing chronic-spontaneous urticaria (p=0.05).

benefit	total	co-existing chronic-spontaneous urticaria	
		no	yes
good or very good	24 (77 %)	14 (93 %)	10 (63 %)
poor	7 (23 %)	1 (7 %)	6 (37 %)
sum	31 (100 %)	15 (48 %)	16 (52 %)

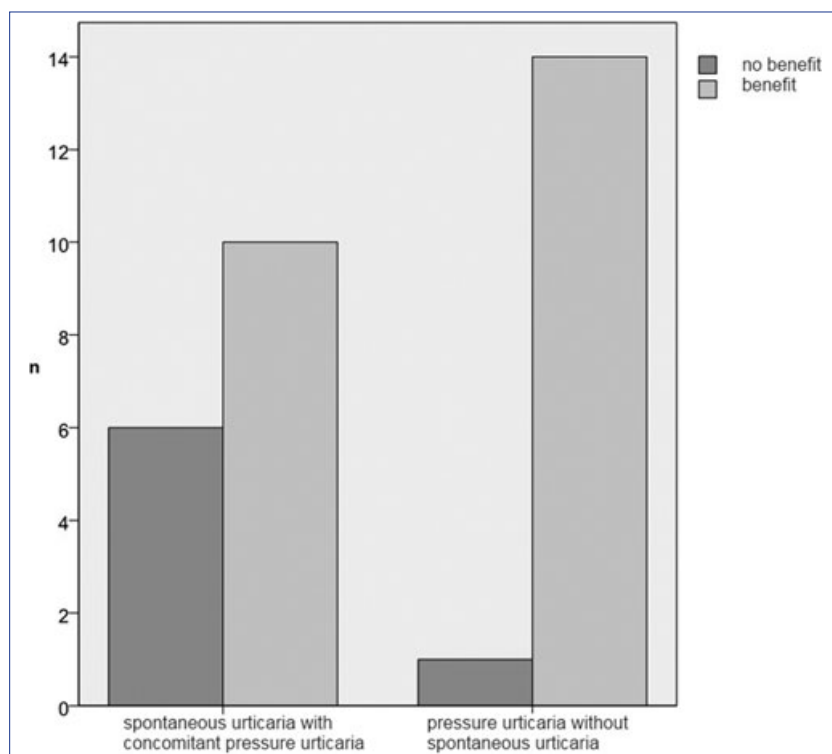


Figure 2: Benefit in patients with co-existing chronic spontaneous urticaria.

response in men and in the age group of 41–55-year olds (Table 4).

The rate of treatment success in patients with side effects or with Met-Hb elevations was 13 % and 44 % lower (Table 5), but there were no significant associations. The greatest treatment response (90 %) was related to treatment durations of 8–12 weeks (Table 6), although the difference compared with shorter or longer durations was not significant.

The duration of disease had a significant effect on treatment success. The treatment response was related to having a short history of disease before starting dapsone (<3 years), although even patients with disease lasting >6 years had a higher than average rate of success (Table 6). The duration of disease among treated patients was on average 3.6 (0.5–26) years.

Discussion

We performed a retrospective analysis on the efficacy of dapsone in treatment-resistant pressure urticaria and chronic spontaneous urticaria with pressure components. Pressure urticaria, caused by vertical application of pressure, has a spontaneous course, usually lasting several years. Symptomatic and immunomodulatory therapies are generally unsuccessful. Most of our patients also had a long history of disease and impaired quality of life despite the use of alternative therapy options. Dapsone therapy was initiated in 31 out of 64 patients who were diagnosed with pressure urticaria at our clinic.

The duration of disease and the co-existence of chronic spontaneous urticaria had a significant influence on the treatment response to dapsone. Nearly 50 % of patients who were given dapsone had both chronic spontaneous urticaria and pressure urticaria. Ergin and colleagues reported in 2008 on the efficacy of dapsone in chronic idiopathic urticaria, which was included in the guidelines [9, 14]. In our patients, dapsone therapy was found to be significantly superior in isolated pressure urticaria. Yet it to what extent this indicates a specific effect is still mere speculation. It is also unclear whether in patients with accompanying chronic spontaneous urticaria other mechanisms such as autoreactivity play a role and are thus the reason for the treatment resistance. This aspect should be included in prospective studies. In regard

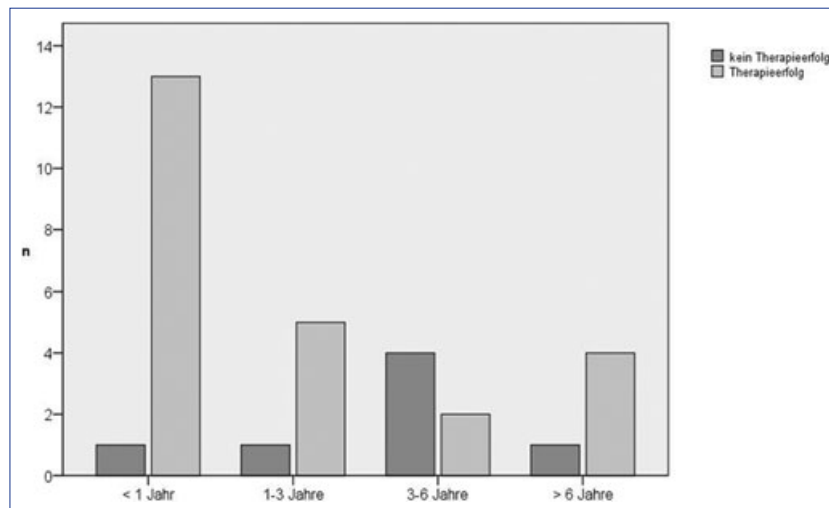


Figure 3: Benefit related to the duration of pressure urticaria.

to the duration of disease, the treatment response was greatest in patients who had a history of disease of less than one year, although even patients with the disease for more than 6 years responded to therapy. Whether this constitutes a res-

ponse to treatment or simply spontaneous healing cannot be clarified here with certainty. Yet the success rates suggest that even patients with longer-term disease and may be given dapsone successfully. Although patients with isolated

pressure urticaria have a significantly higher treatment response than patients with accompanying spontaneous urticaria, the success rate is 63 %, and thus this is also a target group which may benefit from dapsone therapy. Given the sample size, no significant associations were found between a positive or negative treatment response and age, sex, treatment duration, side effects, or elevated Met-Hb. There was, however, a trend to a poorer treatment response in middle-aged patients and in men. Shorter therapy regimens (<7 weeks) were related to a poor response, but side effects and elevated methemoglobin were also related to a poorer treatment response which may be explained by non-compliance or discontinuation of treatment.

To summarize, the treatment regimens described here were well tolerated and achieved a good level of success which was sustained after stopping dapsone. Given the rarity of this disease, we suggest that the effects of dapsone therapy be studied in prospective multi-center

Table 4: Age- and gender-dependent benefit of dapsone therapy.

benefit	total	Age (categorized) in years				sex	
		<= 25	26–40	41–55	56+	female	male
good or very good	24 (77 %)	3 (100 %)	10 (77 %)	10 (71 %)	1 (100 %)	17 (81 %)	7 (70 %)
poor	7 (23 %)	- (0 %)	3 (23 %)	4 (29 %)	- (0 %)	4 (19 %)	3 (30 %)
sum	31 (100 %)	3 (100 %)	13 (100 %)	14 (100 %)	1 (100 %)	21 (100 %)	10 (100 %)

Table 5: Influence of side effects or Met-Hb elevation on therapeutic benefit of dapsone therapy.

benefit	total	side effects		Met Hb elevation	
		no	yes	no	yes
good or very good	24 (77 %)	17 (85 %)	7 (64 %)	23 (82 %)	1 (33 %)
poor	7 (23 %)	3 (15 %)	4 (36 %)	5 (18 %)	2 (67 %)
sum	31 (100 %)	20 (100 %)	11 (100 %)	28 (100 %)	3 (100 %)

Table 6: Influence of length of dapsone use and duration of pressure urticaria on therapeutic benefit.

benefit	sum	therapy with dapsone			duration of pressure urticaria			
		<= 7 weeks	8–12 weeks	>12 weeks	< 1 year	1–3 years	3–6 years	> 6 years
good or very good	24 (77 %)	6 (55 %)	10 (91 %)	8 (89 %)	13 (93 %)	5 (83 %)	2 (33 %)	4 (80 %)
poor	7 (23 %)	5 (45 %)	11 (9 %)	1 (11 %)	1 (7 %)	1 (17 %)	4 (67 %)	1 (20 %)
sum	31 (100 %)	11 (100 %)	11 (100 %)	9 (100 %)	14 (100 %)	6 (100 %)	6 (100 %)	5 (100 %)

analyses so that in the future, targeted treatment recommendations may be made and adapted to individual needs. Even without additional data, we support more widespread use of dapsone given the resistant nature of this disease (especially isolated pressure urticaria). In view of the high rates of success, we believe that treatment based on the above-mentioned scheme for about 3 months is justifiable and would enable the majority of patients to have the shortest duration of treatment possible. If the disease recurs after 3 months of therapy, treatment may begin again. Although the mechanisms of action of sulfone derivatives in pressure urticaria are uncertain, we believe that with adequate monitoring the risk-to-benefit ratio of dapsone therapy in treatment-resistant forms is so impressive that it warrants early treatment initiation. <<<

Conflict of interest

None.

Correspondence to

Sonja A. Grundmann
Klinik und Poliklinik für Hautkrankheiten
Universitätsklinikum Münster
Von-Esmarch-Str. 58
D-48149 Münster
Tel.: +49-251-835 6506
Fax: +49-251-835 8534
E-mail:
sonja.grundmann@ukmuenster.de

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