

Terfenadine once daily in chronic urticaria

A multi-centre double-blind comparison of terfenadine once daily versus twice daily*

The objective of these three double-blind multi-centre studies was to determine whether terfenadine 120 mg once daily has similar efficacy and tolerability as the standard dosage of 60 mg twice daily in the treatment of chronic urticaria. A total of 252 patients were randomly allocated to two parallel groups and treated for 2 weeks with either regimen. Evaluation of efficacy was based on rating scales for investigator and patient, i.e. itch, number of wheals, wheal size and an overall rating of efficacy. A similar improvement was seen in all variables, and there were no statistically significant differences between treatment groups. The power of the studies combined is > 80 %, i.e. sufficient to state convincingly that treatment effects are not different. Both treatments were also equally well tolerated.

Key words: chronic urticaria; clinical study; dosage; double-blind; terfenadine.

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A well-established dosage of terfenadine for the treatment of allergic rhinitis and chronic urticaria is 60 mg twice daily (9). More recently, it has been demonstrated in histamine wheal inhibition tests that 120 mg of terfenadine is effective for 24 h (8), and it has also been shown in the treatment of hay fever that terfenadine 120 mg once daily is as effective and well tolerated as terfenadine 60 mg twice daily (6).

Consequently, a once daily dosage could be expected to be effective in the treatment of chronic urticaria. To test this hypothesis a series of studies was carried out in France, Germany, and Italy.

Results of individual studies have been presented at the Annual Meeting of the European Academy of Allergology and Clinical Immunology in Copenhagen 1988 (5, 7).

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This report is an attempt to evaluate aspects common to all three studies.

METHODS

Study design and treatments

The studies followed a similar protocol, i.e. double-blind comparisons in two parallel groups. Patients were randomly allocated to one of the two groups, according to a computer generated code list (stratification in blocks of 4).

Patients were treated for 2 weeks with terfenadine either 120 mg once daily or 60 mg twice daily. The double-dummy medication comprised tablets of 60 mg terfenadine and identical placebo tablets. Each patient received three bottles containing 17 tablets, and was instructed to take mornings one tablet each of bottle A and B, and evenings one tablet of bottle C.

No additional anti-allergy medication was allowed. Other concomitant medication unlikely to affect the CNS was permitted as long as it was noted in the case report form and maintained at the same dosage throughout the study.

Patient selection

Patients suffering from chronic urticaria were admitted, provided they met the following criteria: age at least 12 years; pregnancy or lactation neither present nor expected; no severe concomitant diseases; no concomitant intake of CNS-active drug; no pretreatment with astemizole, or at least 1 month wash-out; if pretreated with other antihistamines, wash-out for at least 3 days or until symptoms have recurred; if pretreated with corticosteroids, wash-out for 1 month (study C), or for 1 week in case of oral therapy and 6 weeks in case of parenteral therapy (study A); if untreated, symptoms had to be present for at least 8 weeks. In addition, concomitant use of H₂-antagonists was excluded, and patients had to be known to respond to antihistamines (study A).

Table 1
Demographic data and preceding therapy

		Terfenadine 120 mg once daily <i>n</i> = 125	Terfenadine 60 mg twice daily <i>n</i> = 127
Age	mean (SD)	38 (15)	39 (16)
Sex	m	51	56
	f	74	71
Preceding therapy:	terfenadine	32	27
	other	61	63
	none	31	35
	missing information	1	2

Assessments

Although the primary assessments were similar in all three studies some of the rating scales had to be transformed to allow direct comparisons. Itch, for example, was rated in two studies on a 4-point rating scale, whereas in study A a visual analogue scale was used. The latter was transformed as follows: 0–5 mm = no itch (score 1), 6–33 mm = mild itch only (score 2), 34–66 mm = moderate itch with scratches (score 3) and 67–100 mm = unbearable itch with severe scratches (score 4). The distributions of the ratings in each of the three studies were then compared and found to be similar: score 1 (7%, 0%, 5%), score 2 (37%, 35%, 24%), score 3 (42%, 44%, 54%), score 4 (14%, 21%, 16%).

Number and size of wheals were rated by investigator in all three studies on the same 4-point rating scale. Overall efficacy rated on 2-, 4- and 5-point rating scales was reclassified into two classes, i.e. satisfactory and unsatisfactory. An additional efficacy rating vs. the preceding therapy was carried out in all studies (same rating scale: superior, equal, inferior). Further assessments included adverse events, and demographical data.

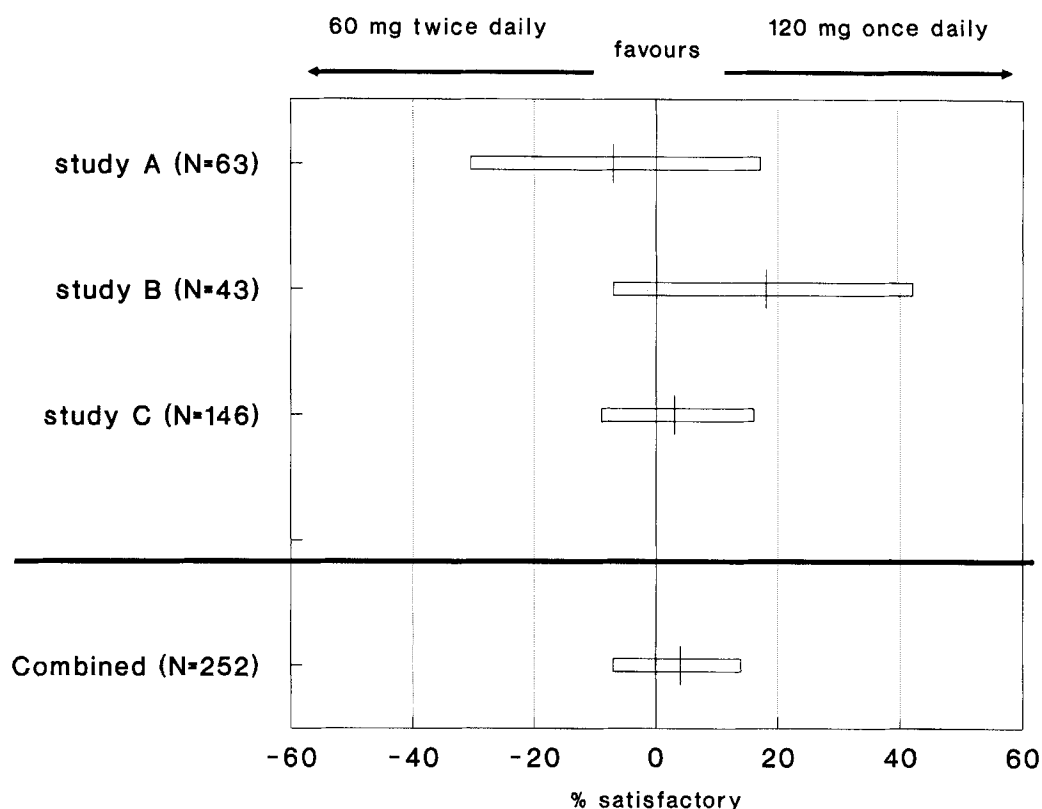


Fig. 1. Differences between proportions of efficacy (percent satisfactory) in the two groups treated for 2 weeks with either terfenadine 120 mg once daily ($n = 125$) or 60 mg twice daily ($n = 127$). Differences and 95%-confidence intervals for each study and the studies combined are shown.

Statistics

An approximate sample size was calculated based on results of previous studies with terfenadine in chronic urticaria (1, 3, 4). A response rate of about 80% was expected and a 20% difference in response rates was to be detected with 80% probability ($\alpha = 0.05$, two-tailed), which requires a sample size of at least 150 patients (2).

Endpoints for the evaluation of efficacy were the ratings of itch, numbers of wheals, wheal size and overall efficacy. Differences between treatment groups at the end of therapy were tested by the Mantel Haenszel test using pre-treatment assessments for covariate adjustment ("test" software, idv in Gauting, Germany).

Two-sided probabilities are given for all tests. Differences between studies were examined in the analysis of overall efficacy by comparing 95%-confidence intervals.

Ethics

All three studies were carried out in accordance with the Declaration of Helsinki (Venice revision 1983 and the laws of each country). Patients were informed about nature, objectives, benefits and risks of the study, and verbal consent was obtained.

RESULTS

Patients were recruited between December 1986 and September 1987, i.e. 43 for study A, 63 for

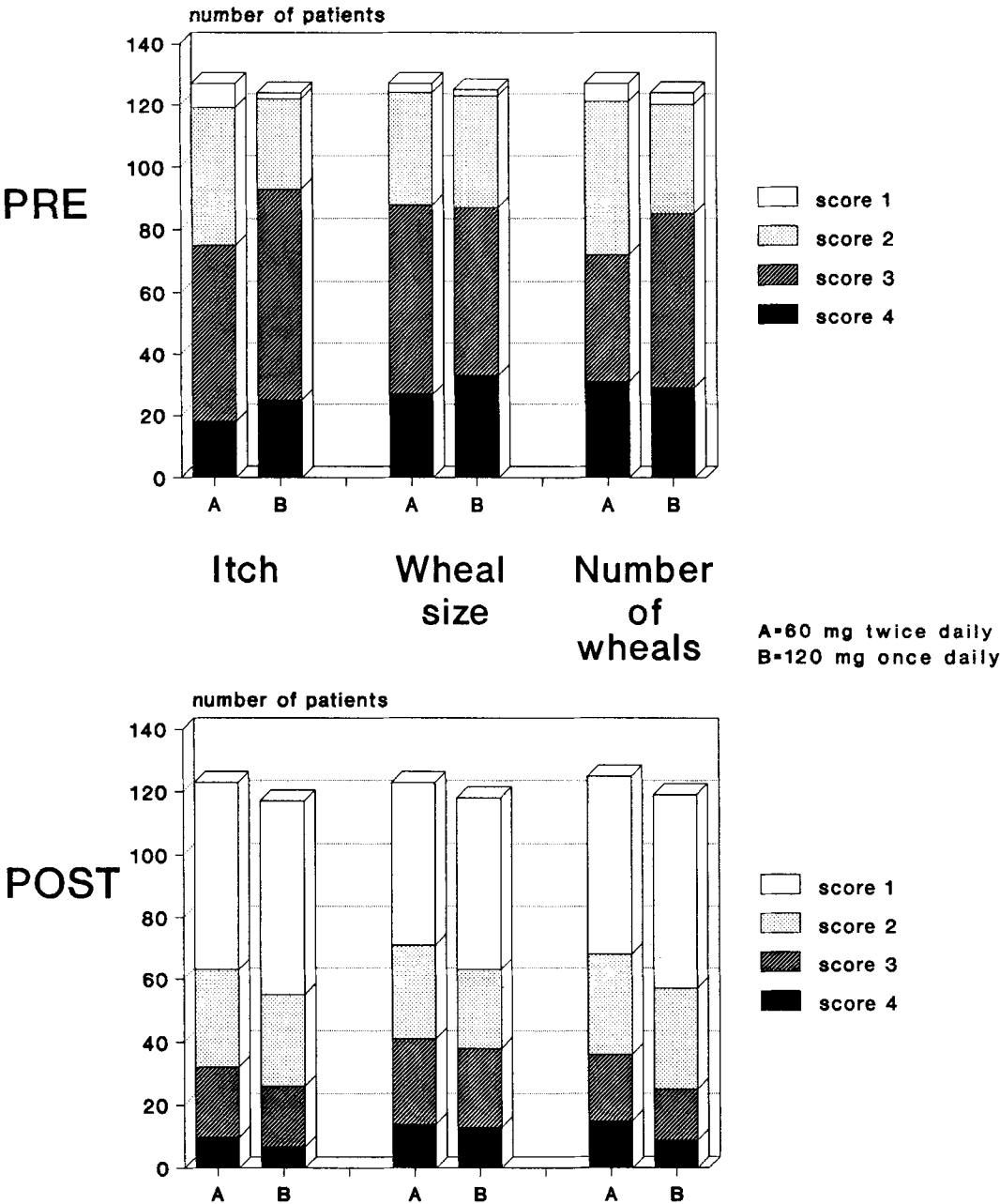
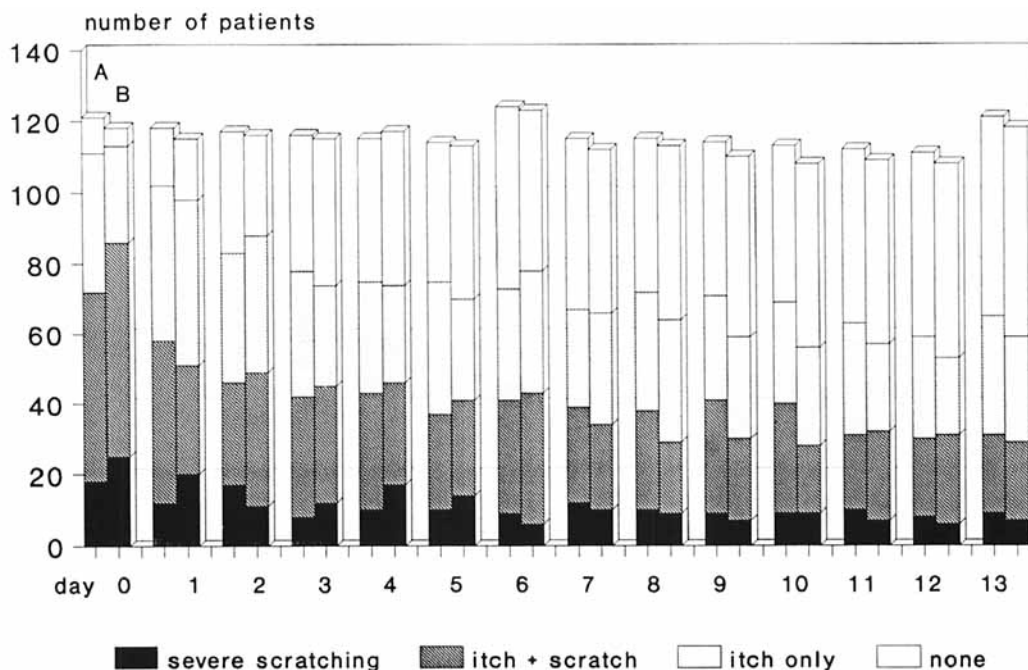


Fig. 2. Frequencies of itch, wheal size and number of wheals, before and after 2 weeks therapy with either terfenadine 120 mg once daily ($n = 125$) or 60 mg twice daily ($n = 127$). The following rating scales were used: itch (score 1 = no itch, score 2 = itch only, score 3 = itch + scratch, score 4 = severe scratching); wheal size (score 1 = 0 mm, score 2 = 1–5 mm, score 3 = 6–15 mm, score 4 = > 15 mm); number of wheals (score 1 = 0, score 2 = 1–10, score 3 = 11–30, score 4 = > 30).

study B and 146 for study C. Of the 252 patients, 125 received terfenadine 120 mg once daily and 127 terfenadine 60 mg twice daily. Demographic data and preceding therapy are



A=60 mg twice daily; B=120 mg once daily

Fig. 3. Frequency of itch ratings over the 2 weeks treatment period in patients treated with either terfenadine 120 mg once daily ($n = 125$) or 60 mg twice daily ($n = 127$).

listed in Table 1 and the severity of symptoms at admission is shown in Fig. 2.

Eight patients (4 in each treatment group) took corticosteroids and two patients astemizole (1 in each group) prior to and/or during the study. One patient of the 120 mg once daily group took an additional antihistamine during the study. Twelve patients (6 of each group) withdrew from the study early for various reasons: insufficient efficacy ($n = 6$), adverse events ($n = 3$), and both ($n = 1$). None of these cases was excluded from the analysis.

Efficacy was rated "satisfactory" in 96 (79%) of the 120 mg once daily group and 93 (75%) of the 60 mg twice daily group (3 ratings were missing in each group). The difference between these two proportions is 7% with an approximate 95%-confidence interval of -7% to 14% (Fig. 1). Intervals of all studies include zero, i.e. differences are not significant. The power of

the studies combined based on these ratings is 87% ($\alpha = 0.05$).

Efficacy of the study treatment was also compared to the preceding therapy which in 59 cases was terfenadine (usually 60 mg twice daily). In the 120 mg once daily group, efficacy of the study treatment was considered superior by 16 patients, about equal by 10 and inferior by 6 patients. Respective numbers in the 60 mg twice daily group are 10, 14 and 3.

Ratings of itch, size and number of wheals show a similar improvement in both treatment groups (Fig. 2). Differences between groups at the end of therapy are small and not significant (Mantel-Haenszel adjusted for pretreatment assessments: $P = 0.13, 0.53$ and 0.6 respectively).

Daily itch ratings by patients depicted in Fig. 3 show that itch severity decreased in both groups steadily and to a similar degree.

Adverse events were reported in 17 cases (7%); 7 in the 120 mg once daily group and 10 in the 60 mg twice daily group. They included gastrointestinal disturbances ($n = 8$), vertigo/dizziness ($n = 2$), fatigue or somnolence ($n = 2$), and in one case each headache, abdominal pain/somnolence, dizziness/palpitation/nausea, microhematomata and cough/dysphagia/pares-thesia. The study drug was discontinued in three cases. All patients recovered.

DISCUSSION

The results indicate that terfenadine 120 mg once daily is about as effective as 60 mg twice daily. This was expected since the results of a skin wheal (8) and a hay fever study (6) have already shown the two dosages to be about equivalent, and since terfenadine 60 mg twice daily is known to be effective in chronic urticaria (1, 3, 4). The response rate was in a similar range (75 to 80%) as in these studies, and itch and wheals were improved to a similar degree. Both treatments were also equally well tolerated.

Although the three studies did not follow the same protocol, they were essentially similar, and so was the outcome. The success rate varied from study to study; however, the differences between the two treatment groups were always small, and the 95%-confidence overlapping and including zero, i.e. there were no significant differences between treatment groups or studies. It seemed therefore permissible to pool the data in order to increase power to 80%.

Deviations from protocol that occurred may have influenced the outcome in some cases. However, the deviations were similarly distributed between treatment groups and therefore should not have affected the hypothesis testing, which was based on the comparison of the two groups.

In conclusion, terfenadine 120 mg taken once daily seems to be a valid alternative to the standard twice daily dosage.

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