Correlations between dose, plasma concentrations, and antispastic action of tizanidine (Sirdalud®)

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Abstract
In a double blind, placebo controlled, cross over study the correlations between single doses (2, 4, and 8 mg), plasma concentrations, and antispastic action of tizanidine were investigated in 16 patients with extensor spasticity of the legs due to multiple sclerosis. An electromyogram was used to assess muscle tone at knee extensors, applying Wartenberg's pendulum test. Blood samples, a clinical assessment of muscle tone by the Ashworth scale, and muscle strength by the British Medical Research Council scale were obtained concomitantly. Confirmatory analysis using the change in the relaxation index (R2 value) 1-5 hours after each treatment, showed a statistically significant (p = 0.0123) linear dose-response relation between single doses and antispastic action of tizanidine. Further statistical analysis showed a strong within patient linear correlation between plasma concentrations and antispastic action at 4 and 8 mg doses (p = 0.014 and 0.004 respectively), but only weak between patient correlations. The analysis of the dose-plasma concentration relation showed results consistent with linear pharmacokinetics. The comparison of changes in the R2 ratio with concomitant Ashworth scores showed a significant correlation between the two. It is concluded that there are linear correlations between single doses, plasma concentrations, and antispastic action of tizanidine. Because of the strong within patient but weak between patient correlation between plasma concentrations and antispastic action of tizanidine the effective doses should be determined individually.

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Tizanidine (Sirdalud®) is a centrally active α2 adrenergic receptor agonist with potent myotonolytic action.1-4 The substance was shown to suppress selectively polysynaptic spinal reflexes while sparing the monosynaptic reflexes.5 Clinical investigations have consistently shown an antispastic effect of tizanidine that was associated with little undue muscle weakness,6-9 sometimes associated with an improvement in paresis.10 There is, however, little information on the correlation between the antispastic effect and plasma concentratons of tizanidine.11 We report data on the correlations between single doses, plasma concentrations, and antispastic action of tizanidine in patients with spasticity due to multiple sclerosis, by means of an objective quantitative method and a clinical scale for the assessment of spasticity.

Methods

PATIENT SELECTION
Seventeen patients were entered into the study, but one patient was excluded from further analysis because the baseline severity of spasticity decreased during the study to below that stipulated in the protocol. There were 13 women and four men, mean age 43 (range 24–58) years. All patients had definite multiple sclerosis, diagnosed by clinical criteria and paraclinical investigations. Spasticity had been present for a mean of 70 (range 12–180) months and had been stable for a mean of 17 (range 2–48) months. Extensor spasticity reaching a minimum score of 2 on the Ashworth scale in at least one leg and remaining stable for at least one month was required as an entry criterion. All patients had a baseline score of either 2 or 3 on knee extensors, none had a score of 4, and none of them were bedridden. Patients receiving any drugs with antispastic action, those with significant systemic diseases, local complications, an exacerbation of the disease, or abnormalities in laboratory tests were excluded from the study.

EXPERIMENTAL PROCEDURE

The protocol was approved by the committee on medical ethics of Dundee General Hospitals, and informed consent was obtained from each patient before they entered the trial. Patients were allocated a treatment sequence according to a randomisation schedule based on a latin square design. Each patient received in a double blind, randomised, cross over design single doses of 2 mg, 4 mg and 8 mg of tizanidine and one dose of placebo on four separate days, allowing a wash out period of at least 72 hours between the different doses. Tizanidine and placebo tablets had the same appearance, and each dose contained the same number of tablets with the same appearance to maintain blindness. The examination schedule and content as well as timing of meals were standardised for each patient and across the patients. The medication was taken with a glass of water.
between 8:00 and 9:00 am, 30 minutes before breakfast and after the baseline evaluations had been performed. An indwelling catheter was placed in the cubital vein 30 minutes before the daily baseline evaluations. Blood samples were taken at baseline, 15, and 30 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours after dosing. Plasma tizanidine concentrations were analysed by a specific radioimmunoassay method with a sensitivity of 250 ng/l.

Measurement of Skeletal Muscle Tone
Each patient was given an initial screening assessment at which muscle tone was evaluated for both legs. Thereafter all measurements were performed on the leg that had the higher spasticity score at the knee extensors. The tone of the quadriceps muscle was measured by means of an electrogoniometer and applying the Wartenberg pendulum test. The principle of this test is that the swing pattern of the lower leg, as it swings under the action of gravity, depends on the tone in the quadriceps muscle. A quantified version of the test was reintroduced by Bajd and Vodovnik and is able to distinguish spasticity and rigidity. The following procedure was used for taking a measurement: The patients lay on a couch with the lower legs hanging over the end. The examined leg was indirectly attached to an electrogoniometer (Penny and Giles, Type PGS) so as to measure the angle at the knee by the method described by Bajd and Vodovnik. The lower leg was lifted as near to the horizontal as possible without taking the upper leg off the couch. Having ensured that the leg was relaxed, the lower leg was then released and allowed to swing freely under gravity. The angle samples were sampled for 10 seconds by a 286 PC microcomputer via a CED 1401 intelligent interface (Cambridge Electronic Design). Seven tests were taken at each assessment session. The first swing was for practice and it was not included in the data. Statistics of the assessment data were obtained by calculating the mean value of each variable from the next six tests. During the examination patients were distracted by music played through headphones to maximise muscle relaxation and to standardise experimental conditions. Goniometric assessments were performed at baseline immediately before drug intake and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 8 hours after the drug intake.

Bajd and Vodovnik have proposed that the best quantitative assessment of spasticity is made from the relaxation index, R2, and this has been confirmed by Brown et al. This is the ratio of the amplitude of the first swing of the leg on release to the difference in angle between the start and final resting position (fig 1). The relaxation index R2 was calculated with PC software. The log of the ratio R2 was used for the confirmatory data analysis. Further data were derived from the pendulum swing traces for descriptive and exploratory analysis. The additional measurements were the ratio R1 (the ratio of the amplitude of the first swing to the amplitude of first rebound swing), the maximum velocity on the first swing, the maximum velocity on the first rebound swing, the maximum acceleration on the first swing, and the maximum acceleration on the rebound swing.

Muscle tone was also assessed clinically with the Ashworth scale. Tone of both the knee extensors and flexors was assessed immediately after each series of goniometric measurements. The strength of knee flexor and extensor muscles was also assessed with the British Medical Research Council (BMRC) scale. The systolic and diastolic blood pressures and pulse rate were measured after each goniometric assessment in each session. Any adverse event occurring after drug intake was recorded.

Data Analysis
The concept described by Abt was used to analyse and interpret the data. Three types of statistical analysis were performed, which were predetermined in the study protocol.

Confirmatory data analysis
This analysis was performed to assess the linearity of the dose–effect relation at the expected time of maximum effects (1.5 hours after medication), with the log₁₀ transformed value of the R2 ratio. The individual effects of the four treatment regimens (placebo, 2 mg, 4 mg, and 8 mg of tizanidine) were split into a linear, a quadratic, and a cubic component. These were tested for statistical significance including also the sequence effect (one way analysis of variance (ANOVA), p = 0.05). The dose was transformed as log (1 + d/dₐ), where dₐ was 0 for dₐ (placebo), 2 for dₐ (2 mg), 4 for dₐ (4 mg), and 8 for dₐ (8 mg of tizanidine).
Descriptive data analysis
All goniometric variables and clinical scores obtained after each dose of study medication were compared with those obtained after placebo, at each time point after medication. The evaluations were performed with both actual values and baseline corrected values (differences from baseline on the day of experiment) by means of two way ANOVA for goniometric variables and the Wilcoxon matched pair signed rank test for the clinical scores (p = 0.05).

Exploratory data analysis
In this analysis the linear correlations between plasma concentrations of tizanidine and goniometric variables (difference from placebo in the baseline corrected values) were investigated. Within patient empirical correlation coefficients were tested for difference from zero for each dose, as well as between patient empirical correlation coefficients for each time point and each dose. In addition, dose normalised area under the plasma concentration-time curve (AUC 0-8 hours) and maximum plasma concentrations (Cmax) were compared by means of a two way ANOVA (p = 0.05), and R2 values were compared with the Ashworth score (difference from placebo) by a within patient rank correlation analysis.

Results
DOSE-RESPONSE RELATION
Figure 1 gives examples of goniometric recordings before and after tizanidine. In the confirmatory analysis the log10 of the difference between the R2 ratio at 1-5 hours and the R2 ratio at baseline for that day and a log transformation of the dose was examined by regression analysis (F test). This analysis gave p = 0.0123 for the linear component of the dose-response curve, indicating a statistically significant relation between the dose and antispastic action of tizanidine in the single dose range of 2 to 8 mg, 1-5 hours after medication. As a log transformation was used for both the dose and the R2 ratio, the dose-response relation was considered to be linear (fig 2). There were no non-linear components to this relation, as the quadratic and cubic components of the dose-response curve were not statistically significant (p = 0.413 and 0.708 respectively). In the descriptive data analysis antispastic effects differed from that seen under placebo occurred up to three hours after taking the drug.

Analysis of variance for treatment/period interactions showed no evidence for carry over effects between the two sequences of placebo followed by 8 mg v 8 mg followed by placebo.

PLASMA CONCENTRATION-RESPONSE RELATION
In each patient, linear correlations were calculated for each dose between plasma concentrations and the goniometric variables. Figure 3 gives examples of regression lines between the plasma concentration of tizanidine and concomitant R2 ratios at the 8 mg dose for four patients. For nine of the 16 patients the slope of the regression line was significantly different from zero. Overall within patient correlation analysis between plasma concentration and the difference in the R2 ratios of placebo and active treatment gave a mean correlation coefficient of 0.005 (p = 0.967) for the 2 mg dose, 0.347 (p = 0.014) for the 4 mg dose, and 0.536 (p = 0.004) for the 8 mg dose.

As well as the analysis of within patient correlations, between patient linear correlations between plasma concentrations and the difference in R2 ratios between placebo v active treatment were also calculated. The analysis showed that 14 out of 288 (4.9%) calculated correlations were significant. No p pattern (clustering of significant correlations at a dose, time point, or both) with regard to time after drug treatment or dose dependency of significant locations was found, suggesting that “nominal” significances occurred by chance. This indicated a rather weak relation across subjects between the antispastic effects of tizanidine and plasma concentrations.
DOSE–PLASMA CONCENTRATION RELATION
Plasma concentrations of tizanidine were obtained at 11 standard times in each investigation day. Figure 4 shows the mean drug plasma concentration curves at the three doses. In the exploratory data analysis, the statistical evaluation of dose-normalised area under the curve (AUC) and the maximum concentration (C_{\text{max}}) at the three dose levels examined gave results consistent with linear pharmacokinetics in the dose range used. The variability in the peak plasma concentrations between patients given the same dose of tizanidine was low (36% at 2 mg, 29% at 4 and 8 mg).

CORRELATION BETWEEN ASHWORTH SCORE AND R2 RATIO
The mean change from baseline in Ashworth score two hours after medication was 28% for placebo, 29% for 2 mg, 34% for 4 mg, and 38% for 8 mg. These mean changes, however, must be interpreted with caution given the non-linear nature of the Ashworth scale. The comparison of changes in the R2 value with concomitant changes in the Ashworth score for extensor muscles by means of a within patient rank correlation analysis showed significant correlations between the two variables at all doses, indicating a strong within patient linear correlation between the R2 ratio and Ashworth score for extensor tone (Spearman rank order correlation coefficients 0·327 (p = 0·01) for 2 mg; 0·631 (p = 0·009) for 4 mg, and 0·629 (p = 0·0001) for 8 mg). Similarly, a between patient rank correlation analysis showed that the changes in these two variables significantly correlated with each other at all dose levels. The number of significant correlations increased dose dependently. The R2 ratio and Ashworth score were negatively correlated in both between and within patient correlation analysis—that is, the higher the R2 ratio, the lower the extensor tone on the Ashworth scale.

Muscle strength, as measured by the BMRC scale did not show any detectable decrease in either extensor or flexor muscle strength at any time after any of the doses of tizanidine.

There was a mild decrease in blood pressure (mean 18 mm Hg systolic and 10 mm Hg diastolic pressure) and heart rate (5 beats/min), one to two hours after the 8 mg single dose of tizanidine. Adverse events appeared in a dose dependent manner. Drowsiness was the most frequent adverse event (one patient in the 2 mg, four patients in the 4 mg, nine patients in the 8 mg, and three patients in the placebo group), followed by dry mouth. All adverse events were rated mild to moderate, and there were no severe adverse events. Total number of adverse events as well as the sum of intensity scores peaked around two hours after drug administration, roughly corresponding to the time of maximum plasma concentration.

Discussion
The purpose of this study was to assess the relations between dose, plasma concentrations, and antispastic effects of tizanidine. Spasticity was assessed by an electrogoniometer using Wartenberg's pendulum test, which gives an objective, quantitative assessment of knee extensor muscle tone. On the basis of previous experience the ratio R2 was chosen as the primary outcome measure of efficacy. Confirmatory analysis showed a linear relation between dose and antispastic efficacy of tizanidine in the single dose range of 2 mg to 8 mg, 1·5 hours after drug intake; this was roughly at the time at which the peak plasma concentrations of the drug occurred. In two other studies, the antispastic action of tizanidine was maximum also at 60–90 minutes.11

Within patient correlation analysis of the relation between plasma concentrations of tizanidine and its antispastic effect showed a strong linear relation at the two higher doses. There was also a linear relation between dose and plasma concentration. Thus at the single doses examined there were strong within patient correlations between dose, plasma concentrations, and antispastic efficacy of tizanidine. No clearcut linear correlation, however, was found in the between patient analysis of the relation between plasma concentrations and antispastic effects of tizanidine. These results suggest that at a given plasma concentration the antispastic action of tizanidine may vary from patient to patient. Therefore, to achieve sufficient antispastic efficacy in a given patient, individual effective plasma concentrations should be reached and maintained. As suggested by the weak between patient correlations, the effective unit doses can vary from patient to patient. The effects of the 2 mg dose of tizanidine on
spastic muscle tone did not differ from placebo, so that unit doses higher than 2 mg are likely to be necessary in most patients. This study also showed a good correlation between the clinical scale (Ashworth scale) most often used to assess spasticity and the objective, quantitative measurement of muscle tone by an electrogoniometer. This finding is important as it suggests that used in a standard way (by the same investigator), the Ashworth scale can be reliably used to assess spasticity in large scale clinical studies in which the use of an electrogoniometer may not be possible. Electrogoniometric measurements, however, seemed to be more sensitive than the clinical assessment to the changes in muscle tone, so that small changes may not be detected by the Ashworth scale. The results also suggest that the electrogoniometer can be reliably used to provide quantitative assessment of muscle tone in spasticity.

At doses at which there was a clinically measurable decrease in spastic muscle tone with the Ashworth scale, no clinically detectable decrease in muscle strength was found on the BMRC scale. This suggests that the antispastic action of tizanidine is not associated with any undue muscle weakness. In fact, in some patients an antiparetic effect was associated with the antispastic effect of tizanidine. It must be borne in mind, however, that the BMRC scale may not be sensitive enough to measure slight changes in muscle strength.

Single doses of tizanidine up to 8 mg were well tolerated. The adverse event profile did not differ from that known from previous experience. The most frequent adverse event was mild drowsiness. The frequency and severity of adverse events increased in a roughly dose-dependent manner and peaked around the time of maximum plasma concentration. This suggests that adverse events may be related to peak plasma concentrations.

It is concluded that there is a linear relation between single doses, plasma concentrations, and antispastic effects of tizanidine in the 2–8 mg dose range. This relation is especially strong in within patient comparisons—that is, in a given patient the antispastic effect is closely related to plasma concentrations of tizanidine. The between patient correlations between plasma concentrations and antispastic effects seem to be less pronounced; thus a certain plasma concentration does not always lead to the same amount of muscle relaxation in all patients. Because a close within patient relation between dose, plasma concentration, and efficacy was found, the effective doses of tizanidine should be determined individually for each patient. The unit doses and dose intervals should be chosen so as to maintain an effective plasma concentration.