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Defining small differences in efficacy between anti-Parkinsonian agents using gait analysis: a comparison of two controlled release formulations of levodopa/decarboxylase inhibitor

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1 Stride length is highly relevant to mobility and is sensitive to the effects of levodopa in Parkinsonism. Its selection as the primary outcome criterion allowed comparison of two levodopa/decarboxylase inhibitor formulations using a small number of subjects.

2 It is also desirable to improve stability. An instrumental method, based on infrared telemetry, has been developed which obtains both distance/time measures of gait and broadness of base, as measured by foot separation at mid-swing. The latter was used as a subsidiary outcome criterion.

3 Nine patients (aged 57 to 77 years) then receiving maintenance therapy for idiopathic Parkinsonism with Sinemet CR alone, but who had previously experienced end of dose effect within 4 h of receiving a dose of a conventional formulation of levodopa/decarboxylase inhibitor, were studied.

4 They received, in random order and at least 4 days apart, single doses of one tablet of Sinemet CR (200 mg levodopa/50 mg carbidopa) and of two capsules of Madopar CR (each 100 mg levodopa/25 mg benserazide), with placebo balance, at 10.00 h. Gait analysis was carried out immediately before and half-hourly for 7 h after a challenge. No routine doses of Sinemet CR were taken between 22.00 h on the night before and 17.00 h on the day of a challenge.

5 Analysis of variance showed a highly significant difference in mean stride length ($P < 0.001$) and in mean foot separation ($P = 0.01$) between serial time points, irrespective of the nature of treatment. There appeared to be a useful therapeutic response to both challenges.

6 There was a significant overall difference in stride length ($P = 0.04$) between the challenges containing active Madopar CR and active Sinemet CR, stride length being, on average, 49 mm ($\simeq$ 5% of the grand mean, 1034 mm) greater for the latter. The difference was best seen 2 h post challenge, when it reached 184 mm ($\simeq$ 18% of corresponding mean, 1013 mm). There was no significant overall difference with respect to foot separation.

7 This methodology makes direct titration of developmental modifications in formulation against a relevant dynamic end point practical. It avoids making erroneous assumptions about performance from the pharmacokinetic profile, and the need to recruit larger numbers of subjects in order to make decisions on the basis of clinical assessments.

Keywords parkinsonism stride length foot separation controlled release levodopa

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Introduction

The sensitivity of distance/time measures of gait, in detecting anti-Parkinsonian treatment effects, has been demonstrated in sufferers without overt 'on/off' fluctuations in performance in relation to individual doses of medication (Bowes *et al.*, 1991). Gait analysis has also proved a powerful tool in detecting changes in responsiveness to medication with duration of therapy, in those with overt fluctuations (Bowes *et al.*, 1992a). Had the most sensitive of the clinical ratings of a cardinal sign used in that study been the primary outcome criterion, nearly five times as many patients would have been required to achieve the same power. Stride length, as well as being sensitive to anti-Parkinsonian treatment effects, is the most discriminant of the basic distance/time measures between those with and without Parkinsonism (Kirollos *et al.*, 1993). The advantages of one currently available anti-Parkinsonism medication over another in treating 'on/off' fluctations are often small: stride length is chosen as the primary outcome criterion in a comparison of the efficacy of two controlled release formulations of levodopa/decaroboxylase inhibitor.

It is, of course, desirable to improve not only mobility, but also stability. However, a direct measure of sway whilst standing does not appear to contribute to a discriminant index for Parkinsonism (Kirollos *et al.*, 1993). Stability depends on the position of the centre of gravity, its distance from the base and the broadness of the latter. An instrumental method has been devised to obtain distance/time measures and foot separation simultaneously, in clinic or ward: Parkinsonian patients who fall do have a narrower foot separation than those who do not (Weller *et al.*, 1992). Foot separation during walking is used here as a subsidiary outcome criterion.

Methods

Patients

Patients of either sex with idiopathic Parkinsonism, who were receiving maintenance therapy with Sinemet CR (Du Pont Pharmaceuticals Ltd), were eligible to enter the study, which had the approval of the local Ethics Committee: informed consent was sought. All had suffered end of dose effect, in the 4 h after a dose of a conventional formulation of levodopa/decarboxylase inhibitor, before Sinemet CR had been prescribed. Those receiving concurrent medication which might potentiate or inhibit a dopaminergic effect were excluded, as were those judged not to be able to complete the trial protocol.

Design

Patients were randomly allocated to receive, at 10.00 h, either one tablet of Sinemet CR (levodopa 200 mg/carbidopa 50 mg) and two capsules of placebo Madopar CR, or two capsules of Madopar CR (Roche Products Ltd, each levodopa 100 mg/benserazide 25 mg) and one tablet of placebo Sinemet CR. The alternate treatment was administered on a separate occasion, at least 4 days after the first.

Light breakfast was taken no later than 08.30 h on a treatment day and no other food given until lunch at 12.30 h, so as not to affect absorption of the test dose. Patients were asked to take no routine doses of Sinemet CR after their 22.00 h dose on the night before, until 17.00 h on a treatment day. Immediately following the final assessment, at 17.00 h, a dose of a conventional levodopa/decarboxylase inhibitor preparation was given. The patient then returned to his/her normal regimen. Should any patient experience a severe or distressing 'end of dose' effect, the procedure would be terminated and the conventional preparation given immediately. Any concurrent therapy was continued unchanged throughout the study.

After a practise, serial gait assessments were carried out immediately before and at half-hourly intervals for 7 h after a challenge.

Gait analysis

The method involves attaching a small device (41 × 28 × 17 mm, 40 g) to the back of the right shoe, a clip to the left shoe, and an infrared based transmitter (80 × 60 × 22 mm, 110 g) at waist level. Figure 1a shows the configuration of the system, and Figure 1b the essential components of the device on the right shoe. A 1200 mm length of fine (0.2 mm diameter) polyester thread (T) is wound on a storage drum (D), mounted on the shaft of a spring motor (SM), its free end being attached to the clip on the left shoe. The spring motor allows the thread to reel to, or from, the drum during walking, and maintains a thread tension of 0.4 N, which is almost imperceptible to the wearer. An optical shaft encoder disc (SED) is mounted on the same shaft as the drum: its angular motion is sensed by a pair of photo interrupters (PI).

A lightweight electrical cable (C) carries signals from the device to the infrared transmitter, which relays information to a receiver mounted close to a laptop computer. The encoding method for data transmission is kept very simple: each slot of the shaft encoder produces a single infrared pulse when rotation is clockwise, and a double pulse when it is anticlockwise. At the receiver, the incoming pulses are stored in a 10 bit up/down counter, the contents of which represent the length of thread between the shoes at any instant. The count, and the direction signal which indicates whether the thread is lengthening or shortening, are downloaded to the computer at a rate of 512 samples s^{-1}. The resolution of the shaft encoder corresponds to a change in thread length of 1 mm. The range of the telemetry system is 50 m (but extendable).

The following mechanism enables the computer program to identify the moving foot. The small plastic guide block (GB), shown in Figure 1b, is lightly biased towards one end of a slot (S) by a small leaf spring (not shown). When the left foot is ahead of the right, the switch contacts (SC) are closed, and the separation of the double pulse is modified to indicate this condition.

Most techniques of gait analysis rely on a fixed reference point, such as the position of a camera, to determine distances moved. The shoestring method

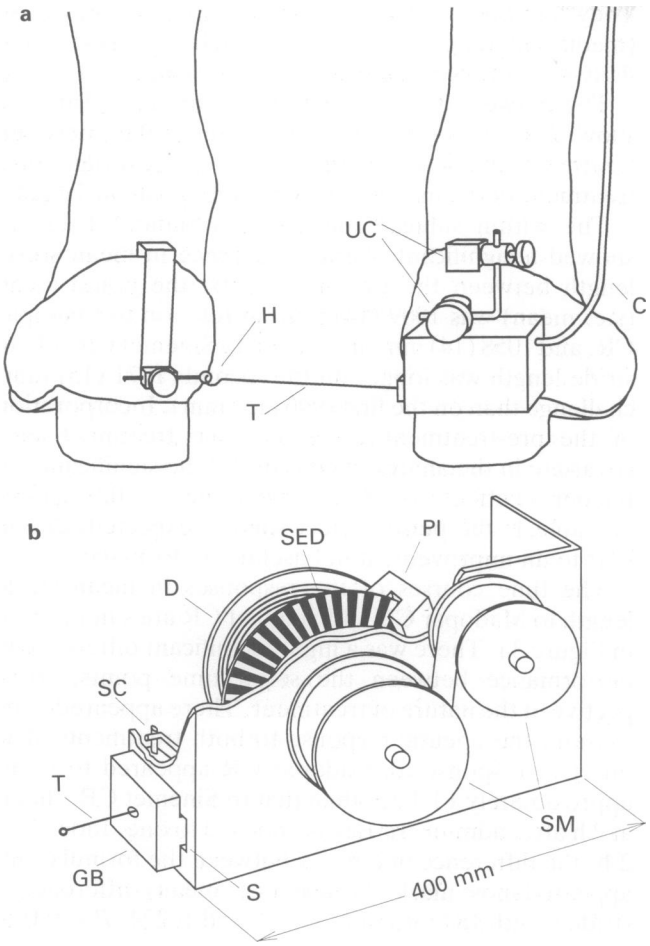

Figure 1 Shoestring device. a) Outline drawing showing positioning of the device (T = thread, H = hook, UC = universal clamp, C = cable). b) The heel-mounted device, with the cover plates removed and part of the U-section chassis cut away (T = thread, GB = guide block, S = slot, SC = switch contacts, D = drum, SED = shaft encoder disc, PI = photo interrupter (one of pair), SM = spring motor).

uses a series of reference points, created by ground-contacts of the feet of the ambulant patient. The length of the thread is monitored throughout the walk. A plan view of the thread when both feet are in ground-contact during walking would take the form of a zig-zag. The thread length is at a minimum as the feet pass each other. Assuming that the feet move in straight lines, coordinate geometry is then used to calculate the distances moved by each foot. It can be shown that curvature of the actual foot paths only introduces errors of a magnitude that warrants correction where gross anatomical abnormalities are present.

In order to allow thread length at mid-swing to be converted, by the program, to separation between the mid-lines of the two heels, manual measurements, made in the start position, are entered. Firstly, the position of the hook (H) (Figure 1a) is adjusted, and the universal clamp (UC) is used to set the position of the guide block, so that the hook and guide block are in line with the most medial aspect of left and right shoe, respectively. Mid-heel separation at rest is then given by adding the external shoe width to the thread length.

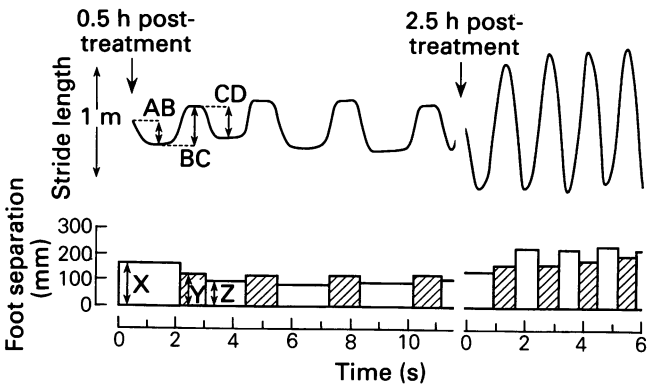

Figure 2 Computer print-outs of graphical representation of distance/time measures of gait and foot separation in the same patient at 0.5 h and 2.5 h after administration of two capsules of Madopar CR. In the upper trace, AB represents the first step, which was with the right foot, BC and CD the first left and right strides. Flattened peaks and troughs are the double support times. In the lower trace, X is the foot separation in the start position, Y and Z the separations at mid-swing of the corresponding strides.

During a walk, the pattern of changing thread lengths is displayed against time to confirm patency of data acquisition. When the walk is completed, the program converts the thread length pattern into distance/time measures of gait and foot separation, which are printed out in graphical (Figure 2) and tabular forms.

Statistical methods

Calculation of sample size Sample size calculations were based on mean stride length being the primary dependent variable and performed using commercially available computer software (N handbook, 1988). If a mean (s.d.) stride length of 1000 (150) mm is taken as being typical, the correlation between the response to both treatments is estimated as 0.95, and the type I and type II errors are set at 0.05 and 0.2, respectively, then a sample size of 10 subjects is required to show a 50 mm (i.e. 5%) difference in mean stride length between treatments. This decreases to five subjects to show a 100 mm (10%) difference.

Statistical analysis The mean stride length for each walk and the mean foot separation at mid swing were used as the dependent variables in an analysis of variance. The corresponding pre-treatment measurements were employed as the covariate in the analysis, in order to increase the precision with which any carry over and treatment effects could be defined, and reduce any difference in performance between first and second periods. On the basis of the pharmacokinetic profiles (Cedarbaum *et al.*, 1989; Crevoisier *et al.*, 1987; Yeh *et al.*, 1989) of the controlled release preparations, the pre-treatment measurement in the second period can be assumed to be unaffected by the previous treatment: adjusting the analysis for this covariate should, therefore, not unduly influence the treatment comparison.

Analysis of variance was performed using Genstat 5 (1989), with an extension of the technique for 2×2 crossover studies. The block structure of the cross-over design was subject/period. That is, period was

nested within subject: period k in one subject is not related to period k in any other subject. This block structure leads to the sums of squares from the analysis of variance being partitioned into three strata, each one having a residual sum of squares against which effects can be evaluated. One stratum is between subject and two strata are within subject, one between, the other within period. The linear model can be expressed using the following notation (McCullagh & Nelder, 1989); 1 + S/P + C + P + T + W*T, where S/P denotes subject/period, C the carry over effect, P the period effect, T the direct treatment effect, and W the effect of time since treatment. The carry over effect is a between subject effect. Both treatment and period effects are within subject, between period effects. The time since treatment effect and the interaction, treatment.time since treatment effect, are within period. This partitioning can be seen in Table 1.

The above analysis assumes a uniform variance-covariance matrix: that is the correlation between measurements made at any two times since treatment is the same. This is not generally the case when there is a repeated measurement. A Greenhouse-Geisser correction factor (Fleiss, 1986) was therefore applied to the degrees of freedom of the serial measurements of gait and the interaction between treatment and time since treatment effects.

The assumptions of normally distributed residuals and equality of variance were investigated using the Shapiro and Wilk's W test (Royston, 1982) and Schweder's (1981) test, respectively.

Results

Nine consecutive patients (six male, three female), receiving Sinemet CR, to be seen in clinic were studied. Their mean (s.d.) age was 67.3 (5.8) years, height 171 (12) cm and weight 69.8 (19.5) kg. The mean time from first diagnosis of Parkinsonism was 11.2 (5.4) years and the mean duration of levodopa therapy 10.3 (4.6) years. They had been taking Sinemet CR for a mean of 386 (median 58, range 9 to 1210) days, their mean (s.d.) total daily dose of levodopa being 894 (240) mg.

The between subject analysis of variance (Table 1) showed there to be no carry over effect between treatments, but a significant effect of the covariate, pre-treatment performance, on both dependent variables.

The within subject analysis of variance (Table 1) showed a significant overall difference in mean stride length between the two treatments: the grand mean (s.e. mean) was 1009 (14) mm, in relation to Madopar CR, and 1058 (14) mm, in relation to Sinemet CR. Mean stride length was longer on the second (1071 (15) mm) challenge than on the first (996 (15) mm). Incorporation of the pre-treatment value for each treatment as a covariate in the analysis had reduced the significance of the period effect from $P = 0.009$ to the $P = 0.01$ shown in Table 1: the period effect was, as expected, due in part to an improvement in baseline performance.

The time courses of the responses in mean stride length to Madopar CR and Sinemet CR are summarised in Figure 3a. There was a highly significant difference in performance between the serial time points, irrespective of the nature of treatment. There appeared to be a useful therapeutic response to both treatments. The onset of response to Madopar CR appeared to occur approximately 1 h later than that to Sinemet CR, that is at 2 h after administration as opposed to one. Indeed, at 2 h, the difference in efficacy between the formulations appeared most marked (mean (s.e. mean) difference in stride length 184 (86) mm, $t = 2.15$, d.f. 224, $P = 0.03$).

The inclusion of two of the nine patients caused the assumptions of normality and of equality of variances to be violated, but the analysis was similar when performed without them. Therefore, the analysis including all nine patients was retained.

There was no significant overall difference in mean foot separation at mid stride between Madopar CR (186 (3) mm) and Sinemet CR (189 (3) mm) treatments, or between first (184 (3) mm) and second (191 (3) mm) challenges (Table 1). However, there was a highly significant difference in foot separation between serial

Table 1 Analysis of variance in mean stride length and in mean foot separation in nine patients, with the respective pre-treatment values as covariate

Source of variation		*Mean stride length*		*Mean foot separation*	
	d.f.	F	P	F	P
Between subject stratum					
period*. treatment**	1,6	0.19	0.7	0.44	0.5
covariate	1,6	41.51	<0.001	69.12	<0.001
Within subject strata between period					
period	1,6	11.99	0.01	2.85	0.1
treatment	1,6	6.42	0.04	0.66	0.4
covariate	1,6	0.67	0.4	0.13	0.7
*within period****					
walk****	4,64	6.18	<0.001	3.47	0.01
treatment . walk	4,64	0.42	0.8	0.84	0.5

* first *c.f.* second treatment.
** Madopar CR *c.f.* Sinemet CR.
*** d.f. corrected to take account of repetition of measurements.
**** *c.f.* serial (1 to 15) half-hourly walks.

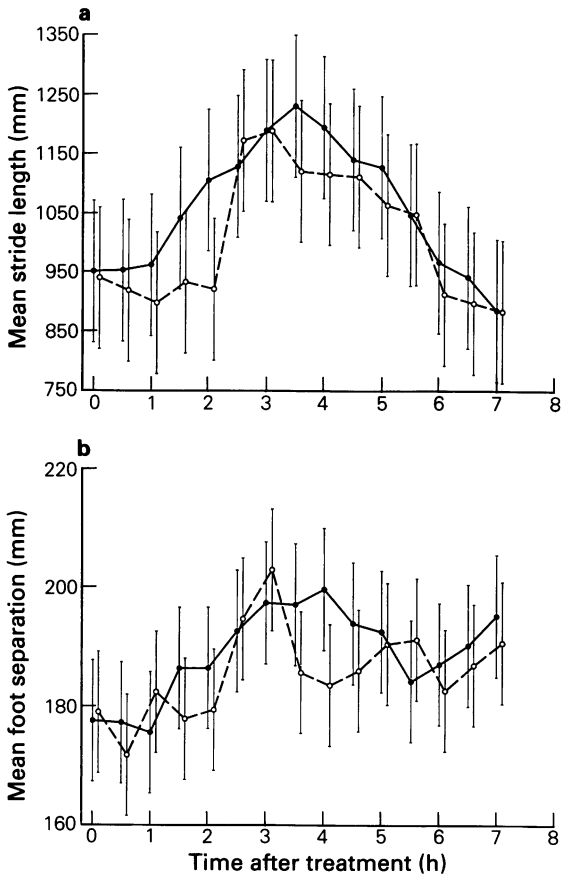

Figure 3 a) Mean stride length and b) mean foot separation at mid-stride immediately before and half-hourly for 7 h after placebo balanced administration of two capsules of active Madopar CR (--o--) and one tablet of active Sinemet CR (—•—). Mean values for the nine patients are given, together with 95% confidence intervals (based on the variance within period, not the between periods variance).

time points, irrespective of nature of treatment. The time course (Figure 3b) indicates that mean foot separation, although not as a sensitive to variations in dosage form as mean stride length, is sensitive to levedopa/decarboxylase inhibitor therapy. The separation had increased by approximately 12% at 3 h post-dose, and there remained an 8% improvement at 7 h.

There was a significant positive correlation between the group mean values, at each of the 15 time points, for mean stride length and mean foot separation ($r = 0.64$, $P = 0.01$ in relation to Madopar CR, and $r = 0.65$, $P = 0.01$ for Sinemet CR). Thus, nearly half the within-patient variance (41%) in the stride length was explained by foot separation during walking.

Discussion

In sufferers from Parkinsonism with motor fluctuations in relation to levodopa therapy, the rationale for continuous dopaminergic stimulation is to produce stable optimal performance. It may also, possibly, minimise deleterious changes at post-synaptic dopamine receptors (Sage & Mark, 1992). Madopar CR (Erni & Held, 1987) and Sinemet CR (Dempski *et al.*, 1989; Wilding *et al.*, 1989) represent two different pharmaceutical approaches to achieving a controlled release formulation for levodopa and a decarboxylase inhibitor. The pharmacokinetics of each of these has been compared with the formulation with conventional release properties from the same manufacturer, confirming sustained release properties. However, delayed time to peak concentrations and/or reduced bioavailability have been reported (Cedarbaum *et al.*, 1989; Crevoisier *et al.*, 1987; Le Witt *et al.*, 1989; Marion *et al.*, 1987; Yeh *et al.*, 1989), and performance may not directly reflect levodopa plasma concentrations with respect to time course or magnitude. Low levodopa concentrations may not be consistently efficacious (Nelson *et al.*, 1990), whilst particularly high concentrations may produce no additional benefit (Bowes *et al.*, 1992a), or may even be associated with deterioration in performance (Bowes *et al.*, 1991; Hughes *et al.*, 1990). The prescriber's concern is primarily with outcome, and there is a need for simple, crossover comparisons of alternatives, designed with this end in mind.

The present study shows Sinemet CR to be preferable to Madopar CR, the former giving, on average, a five per cent (of grand mean) greater mobility, with respect to stride length, over the study period. This was despite there being, on average, little deficit in stride length in relation to height (Dobbs *et al.*, 1993) during 'on' periods. The difference may have been more marked had patients with more advanced disease, and a greater levodopa requirement, been studied using the same test doses.

Turning to the performance/time profiles, previous work in a similar patient group (Bowes *et al.*, 1992a) has shown that the total duration of improvement in mean stride length, from a single, 100 mg levodopa/25 mg carbidopa, tablet with conventional release properties (Sinemet Plus) is, on average, over 4 h. Nearly the full effect was achieved at 1 h. The benefit from one tablet of Sinemet CR of, on average, just over 5 h in the present study, is also in agreement with that previously documented (Bowes *et al.*, 1992a). The time to onset of benefit from one tablet of Sinemet CR was about 1 h in the present study. This compares with the 2 h delay for Madopar CR, followed by improvement in stride length for nearly 4 h. That is, the latter appeared to have a delayed rather than a sustained effect. This led to a marked deficit (18% of grand mean) in stride length 2 h after Madopar CR administration as compared with the same interval after Sinemet CR.

Differences in the bioavailability of the active constituents may, in part, be responsible for the different durations of action of the two CR formulations (Cedarbaum *et al.*, 1989; Crevoisier *et al.*, 1987; Le Witt *et al.*, 1989; Yeh *et al.*, 1989). Increase in dosage may prolong response: over 6 h improvement in mean stride length was obtained after two tablets of Sinemet CR (Bowes *et al.*, 1992a), but the dose ceiling, in those with on/off fluctuations, is usually set by dyskinesia. Some tolerance to the acute effect of levodopa combined with a decarboxylase inhibitor has been demonstrated (Bowes *et al.*, 1992a) and, so, magnitude and/or duration of exposure may be a determinant of duration of benefit from individual doses.

Mean stride length was more sensitive to the effects of levodopa than was mean foot separation at mid-

swing. However, there was a positive correlation between stride length and foot separation, and it may be that the latter is the final arbiter of whether the stride length while walking can be completely normalised. It may be that in some patients a higher dose of levodopa, or a drug with a greater effect on muscle tone and/or the postural abnormality, would be required to produce normal foot separation. In some sufferers abnormalities in foot separation may not have developed, whilst in others the changes may, at least in part, be irreversible. Moreover, where gait is festinant, and of abnormally high cadence (Bowes *et al.*, 1992b), stride length and foot separation may not be positively correlated. It is interesting to note that, although the onset of improvement in stride length and that in foot separation appeared simultaneous, there was a relative lag in return of foot separation to baseline values. Further basic research into the relative time course of action of levodopa on poverty of movement, muscle rigidity and posture may be needed to explain this. Normative data for foot separation during walking is a prerequisite.

Gait analysis methods can range from simple spacial measurements, such as recording the distances between footprints left after dusting a subject's shoes with talcum powder, to sophisticated systems that yield both temporal and three-dimensional spacial data, as well as other relevant physiological signals, such as electromyograms. The simplicity of the former is obviated by the time consuming mensuration, whilst the latter tends to be inordinately expensive, often requiring a purpose-designed building and a team of workers to operate the system and interpret the results. The method described here, like the system from which it was derived (Bowes *et al.*, 1991; Weller *et al.*, 1989), is a compromise. Both furnish the basic components of gait quickly, and at locations convenient for the patient, rather than just to the observer. The newer method can be used in more confined spaces, and gives foot separation whilst walking.

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