Letter to the Editors

Application of a newly designed electronic monitoring device for press through packaging sheets in a clinical trial

Hiroshi Yamada, Shogo Sesoko¹, Takashi Daimon & Mitsuyoshi Nakashima²

Division of Drug Evaluation & Informatics, University of Shizuoka, Shizuoka, ¹Department of Clinical Pharmacology, Maruyama Hospital and ²Hamamatsu Institute of Clinical Pharmacology & Therapeutics, Hamamatsu, Japan

Maintaining good compliance with medication administration is essential in the successful management of clinical trials and clinical practice. Poor compliance to a medication regimen could make it difficult to determine both the efficacy and adverse reactions of the drugs. Therefore, precise monitoring of medication compliance is required for adequate evaluation of intervention for researchers as well as for clinicians.

Various methods have been designed for the measurement of medication compliance, but there have been few reliable tools available. Recently a microprocessor-based Medication Event Monitoring System (MEMS) has been developed for reliable measurement of compliance [1, 2]. However, MEMS depends on opening the lid of the pill bottle when taking the pills, and therefore could not be applied to the pills packaged with press through packaging (PTP) sheets. This is important, especially in countries such as Japan where most prescribed drugs are packaged with PTP sheets and pill bottles are rarely used.

Using a personal computer system for the recording of compliance, we designed an electronic monitoring device for PTP sheets [3]. The device was compact, and easy to carry (Figure 1; weight 120 g, size 72 × 142 × 29 mm; Ohm Electric Co., Hamamatsu, Japan). The pills were easily taken from the bottom side of the device by pushing the button, without the need to open the PTP sheets by hand, and the real dates and times of pushing the button are recorded automatically with a microprocessor in the device. We performed a clinical trial to evaluate the usefulness of this tool to measure medication compliance.

The participants were found from a postmarketing clinical trial conducted by the Japan Pharmacogenomics Consortium (JPGC). JPGC was established by Japanese pharmaceutical industries to collaborate and promote pharmacogenomic clinical trials. One hundred and ten healthy volunteers (men, aged 27 ± 6.3 years, mean $\pm$ SD) were instructed to take a tablet of 81 mg aspirin, the customary dose for Japanese adults on antiplatelet therapy, once daily at 09.00 h for 7 days. They were able to take the device home and took pills for 5 days in their normal life style. On the seventh day of the study, they visited the hospital again and the devices were returned for data retrieval. Counts were made of pills left in the device, and extra pills taken on the same day. Coefficients of variation (CVs) from the indicated medication times were also calculated.

One hundred and nine participants completed the study (Table 1). One man dropped out because of nausea caused by aspirin on the first day of the study, and did not use the device. The device recorded all dates and times of each pushing of the button. The system worked, without the need to open the PTP sheets, and

Figure 1
The device used in the study

Table 1

Summarized results of the study

Number of volunteers participating in the study	110
Age of volunteers, years (mean $\pm$ SD)	27 $\pm$ 6.3
Number of volunteers analysed in the study	109
Number of volunteers who dropped out because of adverse drug reaction	1
Number of real data and times of pushing the button	545
Number of volunteers who left pills in the device	0
Number of volunteers who took extra pills	0
Range of coefficients of variation from the indicated medication times, %	0.01–0.68

seems to be useful for the measurement of medical compliance in clinical trials. The data disclosed no pills left in the device and also no extra pills taken on the same day, and the CVs ranged from 0.01 to 0.68%.

The measurement of compliance consists of two major methods, direct and indirect. Direct methods include observation, biological assays and the use of internal markers, whereas indirect methods include self-report, interview, pill count, clinical response, medication-refill rate and computerized compliance monitors. The different methods measure different aspects of medication compliance and no single method is considered to be entirely reliable. The method described in the study is a microprocessor-based compliance monitor and is indirect. Therefore, a limitation is that it will not detect the participant who pushes the button and discard the pills. For confirming medication compliance, it might be mostly reliable to hospitalize the participants and ascertain their taking medicine in front of investigational staff. However, the approximate cost of hospital stay of 100 volunteers in the study would exceed \$200 000 in Japan compared with that of an ambulatory visit (approximately \$20 000). Therefore the use of the device might have a cost–benefit effect

for the clinical trials sponsors, though compliance should be ascertained by the combination of direct methods such as biological assays or the use of internal markers.

Several factors influence medication compliance, such as dosage, administration schedule, adverse effects, concomitant drugs, age, sex and social behaviour. Medication compliance was very good probably because of several factors, including single daily administration, short administration schedule, low incidence of adverse effects, the participants' young age and motivation to participate in the clinical trial. Further controlled clinical studies should be performed to elucidate whether the device for PTP sheets improves medication compliance in participants of clinical trials as well as in patients who need long-term medication for chronic diseases such as hyperlipidaemia, hypertension or diabetes mellitus.

References

- 1 Cramer JA, Mattson RH, Prevey MI, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA* 1989; 261: 3273–7.
- 2 Kruse W, Weber E. Dynamics of drug regimen compliance – its assessment by microprocessor-based monitoring. *Eur J Clin Pharmacol* 1990; 38: 561–5.
- 3 Yamada H, Nakashima M. New electronic device for monitoring medication compliance. *Am J Health Syst Pharm* 2003; 60: 1910–1.

Received

16 August 2005

Accepted

7 September 2005

Published OnlineEarly

7 November 2005

Correspondence

Hiroshi Yamada MD, PhD, Professor, Division of Drug Evaluation & Informatics, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka, 422-8526, Japan.