

SCIENTIFIC REPORT

Microprocessor controlled compliance monitor for eye drop medication

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Background/aims: The effectiveness of a self administered eye drop medication can only be assessed if the compliance is known. The authors studied the specificity and sensitivity of a new microprocessor controlled monitoring device.

Methods: The monitoring system was conducted by an 8 bit microcontroller for data acquisition and storage with sensors measuring applied pressure to the bottle, temperature, and vertical position. 10 devices were mounted under commercial 10 ml eye drops. Test subjects had to note down each application manually. A total of 15 applications each within 3 days was intended.

Results: Manual reports confirmed 15 applications for each of the 10 bottles. The monitoring devices detected a total of 149 events; one was missed; comprising a sensitivity of 99%. Two devices registered three applications, which did not appear in the manual protocols, indicating a specificity of about 98%. Refrigerated bottles were correctly identified. The battery lifetime exceeded 60 days.

Conclusion: The new monitoring device demonstrated a high reliability of the collected compliance data. The important, yet often unknown, influence of compliance in patient care and clinical trials shall be illuminated by the new device. This may lead to a better adapted patient care. Studies will profit from a higher credibility and results will be less influenced by non-compliance.

Among the many patients receiving eye drop treatment in ophthalmology glaucoma patients constitute the most important group using long term eye drop therapy to lower intraocular pressure (IOP), often in combination with laser therapy or surgery. Although the risk of progression in early manifest glaucoma can be halved by IOP lowering therapy,¹ more than half of newly diagnosed glaucoma patients discontinue all hypotensive topical therapy within 6 months.² Patient non-compliance in the sense of aborting or interrupting potentially effective eye drop treatment is a fact that any ophthalmologist has to consider as a possible reason for treatment failure or illness progression under therapy.^{3–6} When addressing the question of compliance, one usually depends on patients' statements, questionnaires, and personal impressions. In order to learn more about individual patient compliance, we built an affordable medication monitoring system for eye drops with normal appearance suitable for daily usage.

MATERIALS AND METHODS

The apparatus consists of three parts (fig 1), the first part being a conventional eye drop container: usually a 3–10 ml polypropylene squeezing bottle with a diameter of 22–25 mm widely used by the pharmaceutical industry. The second part is a flexible foil pressure sensor that measures the pressure or force applied to the squeezing bottle. The third part is

mounted under the bottom of the eye drop bottle and holds the electronic microcircuitry, battery, and computer interface. All three parts are held together by a flexible transparent shrunk tube. A label is placed inside the shrunk tube to cover the sensors and electronic devices to give the appearance of a normal eye drop bottle.

The functional principles of the monitoring device are summarised in figure 2. The system is conducted by a 8 bit microcontroller (Microchip Technology Inc, Chandler, AZ, USA) using an assembler program which is brought into the system by a chip programmer (Eltec spol. sro, Presov, Slovak Republic) through a cable and stored in program ROM (read only memory). It assures the completion of three main tasks: detection and storage of eye drop application events, management of the system clock, and communication with a personal computer (PC) via interface for data transmission and device configuration.

For the detection of an eye drop application, the unit exploits data from sensors measuring the vertical position of the unit (tilt sensor) and the force applied to the side of the eye drop bottle (pressure sensor) by voltage variation. Additionally, the ambient temperature can be measured. After detection of an eye drop application the data for time, date, and temperature are saved in an EEPROM chip (electrically erasable programmable read only memory). EEPROM data are power blackout safe.

Data transfer to the PC is accomplished through a three wire interface cable. The PC terminal program allows data readout from the EEPROM chip, setting of the system clock, and thresholds, deletion of all data, and system diagnosis.

To evaluate the functionality of the monitoring device, 10 devices were mounted under 10 ml eye drops containing artificial tears (Hypromellose, Sic-OphthalN, Winzer Pharma GmbH, Berlin, Germany) and activated. Each complete monitoring device featured a total weight of 21.5 g including the medication, height 74 mm, and diameter 25 mm (fig 3). Test subjects, recruited from the medical staff at the department of ophthalmology (Cologne, Germany), received bottles after written informed consent and noted each application manually. Bottles had to be carried around with other personal belongings or to be kept in the fridge. A total of 15 applications per bottle was intended. After 3 days all bottles and manual protocols were collected for data analysis.

RESULTS

The collected manual reports indicated 15 applications per bottle, constituting a total of 150 eye drop applications. The electronic protocols read out from compliance monitors showed a total of 149 correctly identified applications. One application was missed; thereby, the observed sensitivity of the apparatus was above 99%. Two devices registered a total of three additional applications that did not appear in the manual protocols, indicating a detection specificity of nearly 98%.

Abbreviations: EEPROM, electrically erasable programmable read only memory; IOP, intraocular pressure; ROM, read only memory



Figure 1 Monitoring device and conventional 5 ml eye drop bottle.

According to the manual and electronic protocols all applications with bottles kept in the fridge before application were identified correctly. After the trial all devices were observed until the battery was exhausted. The observed battery lifetime for the used compliance monitors exceeded 60 days.

DISCUSSION

Many different strategies have been employed to acquire compliance data in the past. Among these the most popular ones were questionnaires, measurements of drug levels in the blood or of blood tracers added to the drug, as well as the analysis of healthcare provider data and electronic monitoring.

Questionnaires and interviews are a common tool in ophthalmology to evaluate compliance with long term treatments.⁷⁻¹⁰ Compliance questionnaires showed a good predictive value compared to electronic medication event monitoring as gold standard.¹¹ But, for the individual patient, this method has an uncertain reliability owing to the dependence on patient's correct self assessment and truthfulness. Additionally, results may be influenced by psychological interactions between patients and medical staff. Though very cheap, questionnaires are not adequate to improve compliance in daily usage.

Analysis of healthcare provider databases, which mostly consist of insurance claims that include demographic, medical, and prescription information, can give information from a large population to the question how often a treatment is being interrupted or aborted after diagnosis²; thus, compliance can be deduced indirectly. Though these data are highly significant for the analysed population, they do not illuminate the individual patient compliance. Furthermore, patients may purchase the prescribed drugs and still not use them properly or regularly. These patients are not assessed by this method.

The measurement of medication blood levels or of blood tracers is not useable with topical therapy in ophthalmology. This method usually gives an impression of compliance only for a limited time period before the measurement, not covering long treatment periods.

Regarding electronic compliance monitoring in ophthalmology, different technologies (table 1) have been described since 1974, beginning with a box recording the removal of a contained eye drop bottle.¹²⁻¹³ The next step was a unit recording the cap removal of an attached 25 ml eye drop bottle in combination with a fluorescein technique to evaluate adequacy of eye drop application.¹⁴ After experiments with a rectangular squeezing bottle,¹⁵ an eye drop bottle with built-in compliance monitoring equipment was described in 1984.¹⁶ It recognised application events by

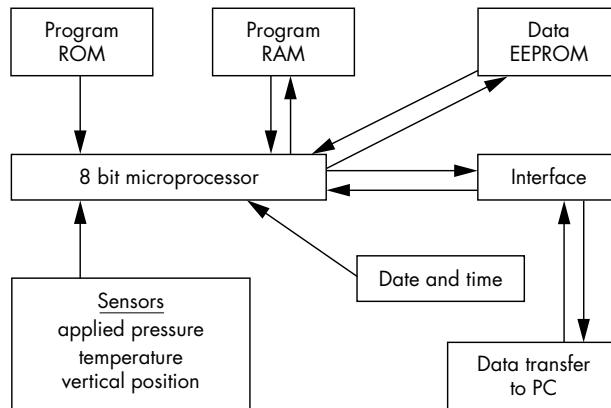


Figure 2 Functional principles of the monitoring device.

detection of cap removal and inversion of the bottle and was used for clinical trials.¹⁷⁻¹⁸ This bottle had to be filled manually with the liquid medication causing additional expense and potential sterility concerns. This unit was not suitable for high volume production, owing to the necessity for new drug packaging and great expense.

The main disadvantages of the methods described were limited usability because of the bulkiness of the devices, complete data loss in case of an empty battery, high cost at the time of presentation, and the fact that the patient was aware of recordings because of the different handling of the compliance monitor compared to a normal bottle. The



Figure 3 Monitoring device mounted under commercial eye drop bottle.

Table 1 Electronic eye drop medication monitors described in the literature compared to the new individual monitoring device

Source, year	Design	Size (mm), weight (g)	Memory	Usability
Yee, ¹² 1974	Box containing medication bottle	100×90×30, 250	Hourly recording, 3 weeks, ram	Unusual appearance and handling for eye drops, does not fit in pocket, uses normal bottles
Kass, ¹⁵ 1978	Rectangular squeeze bottle	109×70×30, 150	15 minute interval, ram	Unusual appearance for eye drops, needs to be filled manually with medication
Norell, ¹⁴ 1980	Box with attached medication bottle	100×50×25, na	Hourly recording, 3 weeks, ram	Unusual appearance and handling for eye drops, does not fit in pocket, uses normal bottles
Kass, ¹⁶ 1984	Squeeze bottle	101×29×29, 52	15 minute interval, 6 weeks, ram	Appearance of unusual 30 ml bottle, fits in pocket, needs to be filled manually with medication
New device, 2005	Squeeze bottle	74×25×25, 21.5 (including medication)	Free intervals, 500 events, EEPROM, battery blackout safe	Usable with any normal 5–10 ml eye drop bottle, fits in pocket, normal appearance with new label

significance of data collected by monitoring devices may be limited by voluntary dyscompliance—that is, the patient empties the eye drops on a regular basis without applying any medication to his eyes. Even the presented device can only report that the patient used his eye drops, but cannot witness that the eye drops reached the eyes.

The new device is free from most of the above mentioned disadvantages. Normal, sealed eye drop bottles are attached to the monitoring device without causing additional sterility or packaging concerns, still preserving the normal appearance of an eye drop bottle. The complete device (fig 3) easily fits in the pocket and should not affect the patient's behaviour. The patients do not have to separate the medication from the electronic device, a possible reason for invalid data or underestimated compliance.

Additional major advantages of the new device are increased data safety, small size and flexibility in usage: data are not lost in case of battery failure, which may occur when patients miss their return appointments. Since the complete operating software can be reprogrammed through the cable interface, the monitoring device may be adapted to the technical needs of trials, patients, or new components such as sensors within seconds. The monitoring unit can be reused after battery replacement. The implemented temperature sensor allows us to evaluate the temperature range to which the unit and the drug are being exposed in daily use. In case of a need for an increased battery lifetime, additional battery capacity may be added to the system. We foresee an option for pharmaceutical mass production and direct patient distribution.

In evidence based treatment studies our device permits us to discriminate between non-responders to medication and non-responders because of patient non-adherence.¹⁹ Thus studies shall profit from a higher credibility with results being less influenced by non-compliance. Besides the assessment of compliance under different conditions and calculation of drug coverage in studies, the monitoring device might be helpful in clinical practice for individual patient care. Less than 25% of glaucoma patients persist with glaucoma therapy over 12 months.³ The assessment of patient compliance also facilitates the decision for additional health care such as home nursing or alternative treatment such as laser or early surgery. Improving the understanding of the individual needs of the patients and their difficulties with eye drops, the most frequently used form of therapy in ophthalmology, will lead to a better adapted patient care.²⁰

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