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NON-ADHERENCE TO PRESCRIBED THERAPY IS A MAJOR OBSTACLE FOR POPULATION PK/PD STUDIES

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BACKGROUND

The extent of non-adherence to prescribed therapy in ambulatory patients is too often overlooked and ignored in the analysis of clinical trials. From clinical studies whose sponsors have concurred with entering their anonymized data into a common database, called PHARMIONIC DATABASE, we have recently finished the assembly and begun the analysis of data on 15214 ambulatory patients whose dosing histories during studies of varying lengths have been electronically compiled.

METHODS

Electronic Medication Event Monitors were used to record the times and dates of drug intake during the course of 87 drug studies performed between 1990 and 2004. Chapter headings in the BritishNational Formulary served to categorize fields of treatment.

Figure 1: Number of patients in the data base for each therapeutic field

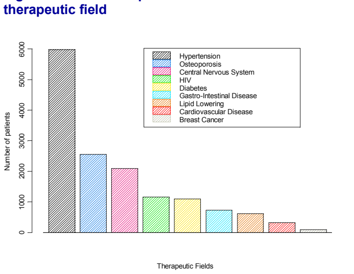
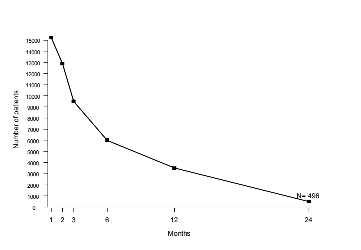


Figure 2: Number of patients in the data base as a function of the follow-up length



RESULTS

Study durations ranged from 30 to 1400 days. Patterns of deviation from prescribed dosing regimens varied widely, but were almost entirely markedly skewed toward longer dosing intervals than prescribed, i.e. under-dosing, in every field of treatment. On average, only during 60% of the study days was the prescribed dosing regimen executed correctly. In studies continuing beyond 6 [12] months, almost 30% [40%] of trial participants had stopped taking the trial medication, despite a prescription that called for continued taking of the drug. Drug holidays (3 or more consecutive days without drug intake) occur at least once a year in 50% of patients. Holidays occur monthly in 2% of the patients, and quarterly in an additional 10% of patients. With QD [BID] regimens, 20% [40%] of doses were not taken on schedule.

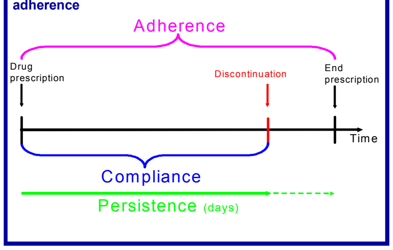
Terminology

Persistence is defined as 'the time in days elapsed between the drug prescription and time of treatment discontinuation'.

Compliance is defined as 'the degree of correspondence between the patient's actual dosing history and the prescribed dosing regimens'.

Adherence is useful as blanket term to subsume persistence and compliance. It is used qualitatively to define 'the patient's tendency to follow medical advice'. 'Poor adherence' signals that something is or was wrong with the patient's use of the drug – not accepted, badly executed and/or discontinued prematurely.

Figure 3: Schematic of persistence, compliance, and adherence



Examples of chronology plots

Patterns of deviation from prescribed dosing regimens varied widely, but were almost entirely markedly skewed toward longer dosing intervals than prescribed, i.e. under-dosing, in every field of treatment. Sample chronology plots illustrating drug intake over time are shown in Figure 4 for four individual patients.

Figure 4: Sample chronology plots

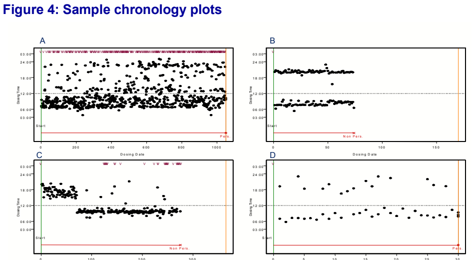


Figure 4A represents a patient who is persistent for almost 3 years. However this patient complies poorly with the assigned QD regimen. Only 75% of prescribed doses are taken. The patterns show a large variability in the time of intake and only 35% of the dose are taken on time.

Figure 4B represents a patient taking all the doses of a BID regimen nearly at the same time but the patient discontinued treatment after 75 days and thus long before the planned end of the follow-up.

Figure 4C represents a patient who switched the intake time from evening to morning. This patient shows long drug holidays (period of time without drug intake) and short persistence, as drug intake was discontinued after 280 days.

Figure 4D represents a patient prescribed a BID regimen for 30 days. The morning dosing is usually correct, but many afternoon doses were missed.

Persistence

In studies continuing beyond 6 [12] months, almost 30% [40%] of trial participants had stopped taking the trial medication. Estimated persistence across the different therapeutic fields is plotted in Figure 5. Figure 6 provides a comparison of the persistence in hypertension with data from the literature.

Figure 5: Persistence estimated across the therapeutic fields

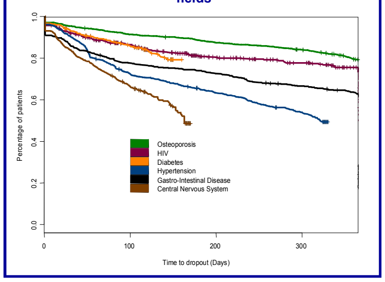
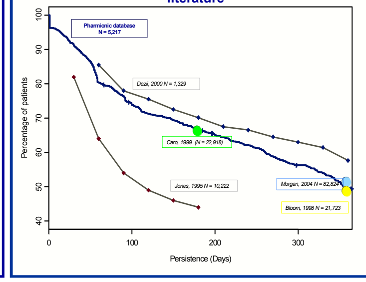


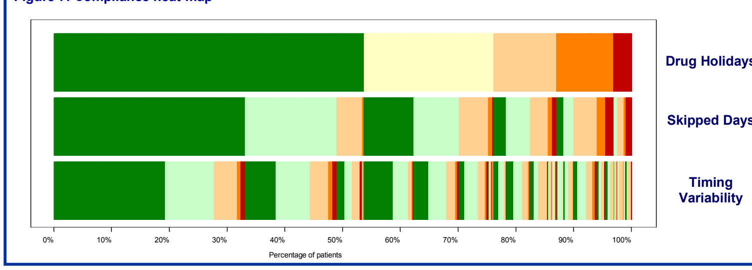
Figure 6: Persistence in hypertension, a review of the literature



Compliance

Ambulatory patients are free to take their medication as they choose, and do so with a great deal of variety. Noncompliance is regarded as the most common cause of nonresponse to medication [1]. Drug holidays, days without intakes, missed doses, variability in the time of intake, underdosing related to the evening dose are common errors reported in the literature. Data from patients under a once daily regimen persistent for at least six months were analyzed. Figure 7 shows a heat-map based on measures of drug holidays, skipped days and the variability of the time of intake. Colors go from green to red: dark green corresponds to a very good compliance whereas red is used to indicate a poor compliance. Each vertical line corresponds to a given patient. This map shows that roughly 19 % of the patients have a perfect compliance and 7 % are extremely poor compliers. The remaining 74 % correspond to a quite complex picture where the best runs alongside with the worst.

Figure 7: Compliance heat-map



A compliance heat-map is an interesting way to display different sources of variability in drug intake. A researcher interested in PK study may argue that those maps provide a dark picture and that the situation is far better during the few days preceding PK samplings. In figure 8, we compare data from case report forms to the ones electronically compiled: the time between the last recorded dose and the first sample is plotted against its reported counterpart. It shows that reported data tend to underestimate the elapsed time. Moreover, 12% of the differences between the reported and recorded intervals are between 1 and 2 hours whereas 18 % exceed two hours. Figure 9 shows the 4 last recorded interdose intervals (D-D) as well as the time between the last intake and the first sample (D-PK). Plain horizontal lines (blue for QD and orange for BID) represent a ideal interdose interval whereas the dashed lines correspond to a time window of ± 2 hours. This plot highlights the extreme variability in drug intake preceding PK samplings.

Figure 8: Discrepancies between CRF and Mems recorded

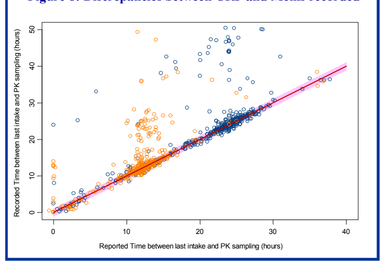
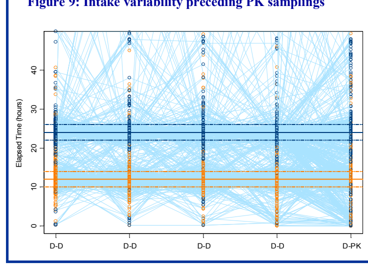


Figure 9: Intake variability preceding PK samplings



The sources of variability highlighted in those figures are usually ignored in PK modeling. Methods have been developed to discard unreliable pharmacokinetic observations [2] leading to a non negligible loss of information. Vrijens et al. [3] have shown that switching from patient-reported to electronically monitored dosing histories improve information derived from population PK studies. This approach typically reduces by more than half the residual variability and avoids any selection bias that could result from the withdrawal of concentration data points.

CONCLUSIONS

Underdosing, drug holidays, and early cessation of dosing are common features of clinical trials, and likely are frequent sources of low response and high variability in response to the protocol-specified dosing regimen. These dosing errors are usually grossly underestimated by counting returned, untaken dosage forms or by asking patients to fill out diaries or questionnaires. In the presence of non-adherence, missing or biased information on the dosage schedule leads to biased PK-PD analysis [4,5] and, more unfortunately, it forces one to discard up to 35 % of collected PK data [2]. The above findings highlight the needs for reliable assessment of dosing histories in clinical trials and impose electronic monitoring as the gold-standard.

References :

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