med-ic® Rx FOR THE THIRD MILLENNIUM

Issue 4 • Spring 2003

INTERPHEX™

SPECIAL REPORT: Focus on Pharmacotherapy

Compliance Monitor

Information Mediary Corporation

Pharmacy as a signal to noise ratio

By Allan Wilson, MD, Ph.D.

Pharmacotherapy may be viewed in terms of a signal to noise ratio (S/N).

In administering any medication, the aim is to maximize the S/N. The signal is the desired clinical effect; the noise comprises a multitude of factors that interfere with, or obscure, the clinical effect.

The clinical effect might be reduction in pain, control of seizures, reduction in white cell count, etc. Most of the myriad noise factors come under the category of 'individual differences' in response to medication. Gastrointestinal differences ranging from mal-absorption to eating habits, differences in metabolism, concomitant use of alcohol and street drugs, body mass, level of activity, use of herbal remedies, and many other noise factors conspire to obscure the therapeutic effect (signal).

The importance of maximizing the S/N is obvious in the area of clinical trials. Clinical trials are designed to determine if the therapeutic effect (S) of an investigational new drug (IND) stands out from all the detracting effects (N) at a significant enough level to warrant approval of the IND by the regulatory body for clinical pharmacy (general use by practitioners).

Analysis of variance, a widely used test of this significance, is simply a ratio of the sum of squares between treatment groups to the sum of squares within groups (F ratio). This is a S/N, where SS between groups is the therapeutic effect (S) and the SS within the obscuring noise (N).

It follows that, in clinical trials, anything that increases the S/NR (F ratio) will speed up recognition of the therapeutic effect of an IND. Higher F ratios in essence result in more rapid approval of useful INDs. They can also have more subtle positive effects such as increasing the accuracy of the dosing regimens developed for a new drug and influencing contraindication profiles.

The idea of S/N extends to general clinical pharmacy – the widespread use of medications that have received regulatory approval. In practice, the physician prescribes a medication for a clinical indication, and watches for the anticipated therapeutic response (the signal). For example, a child with an ear infection might be prescribed an antibiotic to be taken three times daily for 10 days. At the follow-up visit, the physician looks for the signal (a cured infection). If the infection is still present, the physician might reasonably assume that the organism responsible is resistant

Allan Wilson MD Ph.D. is Professor of Psychiatry, University of Ottawa and Director, Substance Use and Concurrent Disorders Program, Royal Ottawa Hospital. He has been involved in clinical pharmacology as a researcher for the last 25 years and has over 100 academic publications to his credit. He co-founded Information Mediary Corporation with Michael Petersen in 2001. IMC is an engineering company that focuses on synergistic problem-solving within the health care field. IMC manufactures the Med-ic® electronic compliance monitor (ECM™) and the eCAP™ electronic bottle cap.

Electronic Compliance Monitoring in Clinical Trials

Electronic Compliance monitors like the Med-ic® ECM™ can be utilized in clinical trials in a variety of ways.

Checking Compliance

The simplest application is where compliance monitoring is used to replace medication diaries and pill counts. The advantages are that the data are more accurate (pill counts and medication diaries are notoriously unreliable for determining patient compliance) and that there are cost savings due to the elimination of time-consuming work by the trials monitor. In addition, the Med-ic® ECM™ incorporates the technical controls to support 21 CFR Part 11 compliance without active input by the trial monitor.

Patient Education During Clinical Trials

It is well-known that education targeted at those who require it is more effective than "broad stroke" education. Although most clinical trials use education to encourage patients to be compliant, it is largely of the broad stroke type. Patients whose medication diaries or pill counts suggest poor compliance may receive targeted education, but it is known that the data obtained by these means are not accurate. In many clinical trials, education can be targeted at noncompliant patients at intervals during the study. With electronic compliance monitoring, noncompliant patients can be indicated to the trial monitor with little extra effort, the data on which the targeting is based will be accurate, and the integrity of the study design will not be jeopardized.

(Continued on page 2)

At Issue: Signal to Noise Ratios

(Continued from page 1)

to the antibiotic prescribed, and might change the patient to a broader spectrum or more potent antibiotic, likely with more potential for toxicity (side effects).

In this example, there are two reasons for the lack of a signal: first, the physician's assumption may be correct – the infection is caused by an organism that cannot be eradicated by the antibiotic used so there is no signal. The second reason is that there really was a therapeutic effect but that it was obscured by noise.

Patient Non-compliance with Prescribed Medication as a Source of Noise

Patient noncompliance with prescribed medication has long been identified as interfering with the therapeutic effect of prescribed medication. This source of noise has been estimated to cost the United States health care system $100,000,000,000 and to be responsible for over 100,000 hospitalization admissions annually (est. for 1996). These statistics are well-known and widely accepted. Within this model, removal of this source of noise would have a significant beneficial effect on increasing the S/N.

Efforts to improve patient compliance with prescribed medication are designed to do this. The oral contraceptive wheel was devised as a means of increasing the therapeutic effect (S) in a clinical setting where noncompliance could have obvious and devastating consequences. Other strategies have been devised to address noncompliance. In clinical trials the medication diary and pill count have been widely used to assess this problem. Blister packaging has evolved at least partially in response to this problem.

The general assumption is that patients are usually noncompliant because they forget to take their medication, not because they have an ulterior agenda to confound the therapeutic process. The corollary is that making medication–taking easier will increase compliance. Although electronic means of monitoring patient compliance have been in the market for the last decade, they have not gained widespread acceptance due to a number of factors including cost, size, and especially the fact they do not integrate seamlessly in the medication-taking process.

Seamless means of monitoring patient compliance electronically, such as the Med-ic® Electronic Compliance Monitor (ECM™) are now coming to the marketplace. Initially, they will prove invaluable in the clinical trials arena, where their ability to increase the S/N by reducing noncompliance can be translated in quantifiable cost savings through speeding up the approval process for INDs. The advantage of the new generation of electronic compliance monitors is that they can be integrated seamlessly into standard blister packages and require no extra effort on the part of the patient.

Med-ic®: Compliance Monitor Utilization

Pre-Testing Patients for Non-compliance

One strategy for increasing patient compliance in clinical trials is to run a placebo pre-trial to determine which patients are compliant. Those demonstrating non-compliance can be targeted for education, and the cohort retested. Once group compliance is at an acceptable level, the patients can be entered in the study. In a variation of this, persistently noncompliant patients might be removed from the sample although this may have profound negative implications for the analysis of the study data and for generalizing the results to the population of interest.

Co-varying for Non-compliant Patients

As our understanding of how non-compliance relates to other factors of interest in clinical trials increases, it may prove possible to co vary out non-compliance as a factor during statistical analysis of study data.

imc | INFORMATION MEDIARY CORP.

About Us

Information Mediary Corporation is dedicated to the convergence of medicine, logistics, high-technology, pharmacology, wireless, e-business and anthroponomy.

IMC's recent flagship Med-ic® and Log-ic™ ECM™ product development efforts underscore this commitment by recognizing and solving important issues. Compliance monitoring has been viewed increasingly as a problem in clinical research and clinical pharmacy over the past decade. Prior to the Med-ic® ECM™ Package there was no user friendly, seamless and accurate solution to the problem.

Contact Us

2150 Thurston Drive, Suite 101
Ottawa, Ontario, Canada K1G 5T9
t: 613.745.8400 x411 f: 613.745.8464
info@informationmediary.com

www.informationmediary.com