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Computer-Assisted Design of Studies Using Routine Clinical Data

Analyzing the Association of Prednisone and Cholesterol

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To facilitate the analysis of routine, longitudinal, clinical data, we developed a computer program called the RX Study Module. Our prototype uses a small online knowledge base of medicine and biostatistics to help create and execute a detailed statistical study design. The program identifies possible confounding variables, selects methods for controlling them, creates a statistical model, determines patient eligibility criteria, and retrieves data from records. We used the program to examine the hypothesis that daily prednisone administration elevates serum cholesterol. Data from 49 patients with chronic rheumatologic disorders were analyzed from a database of 1787 patients. A regression model was fitted to each patient's record. Changes in cholesterol were significantly correlated ($p = 10^{-5}$) with changes in prednisone after a lag of at least 1 week and after recorded confounders were controlled: Δcholesterol $= 18.4 \log_e$(prednisone). Routinely collected patient data may become an important resource for generating and studying new medical hypotheses.

SINCE 1970 when large-scale integrated circuits were first marketed, the capabilities of computers and electronic memories have increased a thousand-fold while their costs have dropped by the same factor. These technologic developments have permitted the increasingly widespread collection of routine, longitudinal clinical data in electronic form. Motivation for recording data electronically comes not only from physicians and other practitioners who desire rapid access to records for patient management and clinical investigation, but also from third-party insurers, hospital administrators, and government agencies. In response to these two factors—the decreasing cost of computing equipment and the increasing demand for detailed and accurate clinical data—a number of software systems have emerged for recording clinical data sequentially as it is routinely gathered in ambulatory clinics. Widely known examples include COSTAR (1, 2), TMR (3), RMIS (4, 5), STOR (6), ARAMIS (7), MEDLOG (8), and CLINFO (9).

Recognizing the growing value of these databases for medical studies, we started work in 1978 on a software package called the RX Study Module. This program is intended to assist a clinical investigator with designing and analyzing a database of routine clinical data. The Study Module facilitates these tasks by assisting with the selection and control of confounding variables, assisting with the design of the mathematical model of the effect of interest, and automating the execution of the study design on a statistical package (10-14).

We will show how the Study Module works using one clinical hypothesis of interest. The study design includes three innovative aspects. First, the study design itself is assembled semi-automatically with the assistance of an online knowledge base of clinical medicine and biostatistics. Second, the resulting study design uses all the relevant data in long-term patient records, taking account of the detailed time relationships among the data. Third, the study design uses a two-stage regression method that enables it to quantitate the effects of drugs within individual patient records and to compare these effects across patients. These methods have not previously been applied to routinely collected, longitudinal clinical data. To demonstrate the methods used by the Study Module we will show the steps used to study the association of prednisone with subsequent increases in serum cholesterol.

The Effect of Prednisone on Cholesterol

Beyond serving as a demonstration of how the basic design of a study may be assisted by computer, the effect of chronic, daily prednisone administration on serum cholesterol is of considerable clinical importance. Prednisone is a potent steroid commonly administered for various chronic disorders. Hypercholesterolemia is a well-established risk factor for atherogenesis and subsequent vascular occlusion. If patients who are chronically taking steroids have elevated serum cholesterol levels they will be at increased risk for accelerated arteriosclerosis, myocardial infarction, and stroke. Indeed, the evidence supporting this relationship is abundant.

Over the past 35 years there have been several published reports showing that chronically administered steroids elevate serum lipoproteins with concomitant increases in serum cholesterol. The first report of this effect in humans appeared in 1950 (15). In 1962, Moran (16), studying the effects of daily, high-dose cortisone in rabbits, found severe hyperlipoproteinemia as well as fatty changes in the liver, kidney, and other organs. Reaven and associates (17) reported that corticosteroid administration in rats increased both plasma triglycerides and cholesterol, caused by accelerated hepatic lipoprotein synthesis. Zimmerman and colleagues (18), in a recent prospective study of 12 patients, found a 17% increase in cholesterol, mainly due to a 68% elevation in high-density lipoprotein cholesterol.

Clinical studies within the past 10 years have focused predominantly on patients who have undergone renal

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