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Evaluation of drug information retrieval services for selected investigational antineoplastic agents

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EVALUATION OF DRUG INFORMATION RETRIEVAL SERVICES FOR SELECTED INVESTIGATIONAL ANTINEOPLASTIC AGENTS

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Contents

List of Tables

Table

Page

Introduction

The availability of drug information that is useful to clinicians is an important need for those responsible for medication use in patients. Physicians, pharmacists, nurses, and patients routinely require access to relevant information related to rational drug therapy. The need for rapid access to relevant information has become increasingly important as the science, technology, and specialization within health care expand. Because of this expansion the literature has increased not only in size but also in complexity.

The term drug information (e.g., used in drug information service, drug information center or drug information specialist) is defined as "knowledge of facts or circumstances acquired through reading, study or practical experience concerning the chemical substance intended for use in diagnosis, prevention, treatment or cure of disease or otherwise to enhance the physical or mental well-being of men or animals" (1). This definition may be expanded to include the ability to provide information to the user in a special manner known as a drug information service. Drug information service is defined as "the activities involved with accumulating, organizing, and retrieving drug information and may include provision of documents and bibliographic compilations or other medical library functions" (1).

Evolution of Drug Literature

In the late 17th century the first scientific periodicals were established to allow the publication of scientific papers in these journals instead of in books (2). In the middle 1930s significant changes in the

numbers of medical agents began with the introduction of sulfonamides in the 1930s and penicillin and other antibiotics in the 1940s (1). The growth of chemistry and biological sciences helped the physician to diagnose disease and to prescribe an increasing number of drugs for disease-specific therapy (3). By 1945 the availability of new synthetic drugs was limited, but between 1948-1960 the increasing number of pharmaceutical manufacturers led to a significant increase in new drugs. Associated with the increased number of drugs was an increase in the volume of medical and pharmaceutical literature (1). A congressional report related to the drug literature was published in 1963 and included the following statements (1, 4, 5):

1. The scientific and medical literature is vast and complex and it is not possible to define the "drug literature."

2. Drug literature includes primary journals, abstracting and indexing publications, books, monographs, patents, proceedings, reviews, package inserts, as well as such related forms as house organs, newsletters, promotional literature, analyses by consultant services, etc.

3. There is no simple or single solution to the "problem" of drug literature because it is really a complex of problems, requiring a complex of efforts for solutions.

Much important drug information is not "published"; information on adverse reactions to drugs, much of which is not published, is a leading example.

5. Competent evaluation of masses of drug information is particularly necessary.

In 1963 the Kefauver-Harris (New Drug) Amendments were published which required that new drugs must be proven safe and effective prior to

receiving Food and Drug Administration approval for marketing. This amendment led to revisions of investigational drug regulations, expanded the need for clinical evaluation of drugs, and greatly increased the drug information literature. For example, it has been estimated that about 2,000,000 new reports related to health care and research are published per year and that 25-50 percent of these reports include information about drugs. Of these, only about 200,000 are in traditional "pharmaceutical" publications (4). The balance of these publications are contained in medical and other clinical publications. To respond to the increase in size and complexity of the drug literature, numerous drug information services and systems have been developed during the past twenty years. Although these services and systems are diverse in design, their objectives are similar and rather simple, and include providing service and education regarding medication use. A principle objective associated with a drug information service is to provide rapid access to relevant information about drug use. The ultimate goal of the service is to help provide answers related to medication use in patients, and includes considerations such as dosage adjustments, drug of choice, pharmacology, side effects, adverse reactions, or interactions. A second objective associated with drug information services is to educate health care providers and patients on rational drug therapy. Physicians, pharmacists, nurses, other health professionals, and patients may participate in seminars, lectures, discussions, or receive publications in order to learn the latest information on appropriate drug use.

Types of Drug Literature

There are three classes of drug literature as follows:

1. Primary literature (sources). These sources are considered the most specific type of information. They appear regularly in journals or "periodicals" and contain the original papers or articles that provide the initial reporting of results of clinical and other investigations. Articles in the primary literature focus on many aspects of drugs, such as drug therapy evaluations, side effects, and adverse reactions. It was estimated that in 1963 the number of world scientific periodicals was 50,000, of which 30,000 are still active. These journals contain about six million scientific papers. The estimated number of papers has increased at a rate of about 500,000 per year, 10 percent of which are biomedical in nature (2).

2. Secondary literature (sources). These sources use various formats and serve as a guide to the primary literature. The examples of secondary literature include abstracting and indexing publications such as International Pharmaceutical Abstracts, Index Medicus, deHaen Drugs In Use and Iowa Drug Information Service. Oatfield and Emilia (6) have listed 75 secondary sources which are helpful in searching the drug literature. Watanabe et al. (7) have mentioned that "secondary reference sources are not necessarily restricted in their scope to certain types of information. Exceptions, however, are Adverse Reaction Titles from the Excerpta Medica Foundation, Clin Alert from Science Editor, Inc. and Toxicity Bibliography from Index Medicus of the National Library of Medicine. These sources are more specific for information on the adverse reactions and toxicities of drugs."

A relatively new type of secondary source is called the automated drug information service. These automated services are designed to provide and use two types of information (8). The information monitoring

type maintains a patient profile that includes all medications taken by the patient. When a new drug is given to the patient, it can be checked automatically by the service to determine if there is a potential for adverse reactions, interactions, or any other problems. The information monitoring type has been developed for use in inpatient as well as ambulatory care settings (9-11). Examples of this type include the systems of Cohen at Stanford University Medical Center (9) and Maronde and Associates at the Los Angeles County-University of Southern California Medical Center (12). The second type of automated services is designed to answer questions. This type has a computerized drug information storage device where the information is stored and is available to the user. By using a combination of key words to define the question, the computer provides one or more possible "answers" to the question. The examples of this type include Excerpta Medica, Drugdoc (EMD) and Medlars.

3. General Reference Works. These sources contain documented information from the primary literature in condensed and compact format. General references provide drug information in specific areas. They do not appear in series at regular intervals so they may not contain current information from the primary literature. In addition general references differ from the secondary literature in format and type. Examples of general references are textbooks, review articles and reference works (7).

Drug Information Needs

1. Physician. One of the major users of drug information is the physician, who must make patient-specific drug therapy decisions. Changing therapeutic approaches and emerging areas of specialty, such as oncology, have placed an increased burden on the physician to seek timely

and appropriate sources of drug information. In many instances clinical pharmacists may serve as the most accessible source of drug information. Specific types of information required by the physician may include choice of therapy, dosage, toxicity, side effects, mechanism of action, interactions and pharmacokinetics. In certain situations the information requested is not easily acquired, e.g., information on investigational drugs. Regardless of the situation, drug literature, manufacturers' material, books, and specialized indices serve as the major sources of information to answer the physicians' questions. A special concern is to use the drug infomration resource that is most effective and efficient for the specific question under consideration. Gaining access to the appropriate source of information on a timely basis is critical if the physician is to respond appropriately to the changing medical needs of the patient. Because of the need for a timely response, using a clinical pharmacist or drug information center as the physician's intermediary has been recommended (1).

2. Pharmacist. The pharmacist's needs for drug information can be related to the following:

A. The usual dosage, commercial availability, stability, storage conditions or price of the prescription medications which he is dispensing. This kind of information is generally termed pharmaceutical and may be obtained from the product manufacturer or from the various publications that specialize in this kind of information. Examples of these include the Physician's Desk Reference, Facts and Comparisons; and

B. Questions which are usually asked by physicians, nurses, patients, and others, about the drug. To answer such questions the pharmacist should have the ability to utilize appropriately any of the

information sources which are available to him. In addition to prescription drug information, the pharmacist has a special and unique need for information on medications available without the physician's prescription (1).

3. Nurses. Levine described the drug information needs of nurses (13). "The nurse should know the expected side effects, and therapeutic risks so that he/she can make intelligent decisions about giving or withholding a drug." The nurse needs to know the dangers of drug therapy, especially those associated with drug administration. In the hospitalized situation the nurse is the last check to insure the patient receives the correct drug and dose at the right time via the correct route.

4. Patient. The patient needs information about the medications he/she is taking. Such things as the drug's effects, how it should be stored, how and when it should be taken, side effects, etc., are important to the successful treatment of the patient. If the patient does not know how to take his/her medications, it is obvious that problems in self-administration may occur. One of these problems is the development of adverse reaction to the drug, which was estimated in 1969 to cause about $1.5 million of hospital annual admissions (14). In 1975, adverse drug reactions were reported to add $3 billion to U.S. health care costs (15).

Pharmacist's Role

The role of the pharmacist as a drug information specialist has expanded as a result of the increasing number of new drugs, and the research reported in the drug literature. This role is not new, for it was described by Irons who wrote in the Journal of the American Medical Association in 1930 that "a closer acquaintance and cooperation between

the hospital pharmacist and the members of the medical staff will be of mutual profit . . . and the pharmacist has not taken as large a place in hospital conferences as he should. His function should not cease with the supplying of drugs called for in a prescription and the detecting of inadvertent errors of dosage, but properly should be extended in an informative and advisory capacity" (16). Another author wrote in 1966 that the role of the pharmacist as a drug information specialist was essentially unfilled (17). Watanabe and Conner in 1978 suggested that the solution to the complex problem of communicating the latest information on drugs and their use by health care practitioners would be to develop clinically trained pharmacists as a source of drug information (7). Halbert et al. in 1977 did a survey of 90 drug information centers and their results showed that pharmacists "fall short in attaining their full potential for producing rapid, accurate and concise information about drugs" (18). A survey prepared for the U.S. Food and Drug Administration indicated that pharmacists were selected as a source for clinical information by less than 20 percent of the responding physicians (19). There are many reasons for this shortcoming. Pearson wrote in 1975 "presently only a few (less than five) programs in this country are devoting a sufficient amount of effort to the training of drug information specialists, and this year at least six major drug information services may not be able to locate and hire qualified specialists. In view of this, it is obvious that the supply is far less than demand" (20). Another reason was indicated by Francke who wrote in 1966 "pharmacy students do not have the opportunity to form a public health oriented self-image because they are not in contact with those who can help them until their course is almost over and then it is almost too late. Pharmacists

need the right type of contact early in their educational process." He also indicated that "students learn not only from didactic instruction of their professors and from the precepts of practitioners; they learn more enduringly from their sustained involvement with the patient, physicians, nurses, dieticians, and other members of the health-care team in an institution devoted to the care of the sick guided by the model of a clinically oriented pharmacist with whom they can readily identify" (21). Zellmer in 1974 suggested that "perhaps it is time for our profession, under some appropriate national leadership to expand the scope of existing drug information centers and create new centers as well. Further, when the profession finally develops a system for certifying specialists, hopefully a specialty in drug information services will be recognized. This would be an important factor in attaining for certain pharmacists recognition as 'highly trained drug consultants'" (22).

In general these studies cited above indicated that in the 1970s the pharmacist's role as a drug information specialist was not fully developed. Since that time several responsibilities have been described as part of the role of the drug information pharmacist. These responsibilities include the following:

1. Identify sources of clinical information in general: references, textbooks, abstracting/indexing services, and scientific journals;
2. Interpret, analyze and evaluate this information;
3. Provide this information to the person who needs it.

Further, in order for the pharmacist to function as a drug information specialist he must enter the clinical area and serve as an interface between the biomedical literature and the clinician and his patient (2). This involvement in the clinical area will increase the physician's response

to the pharmacist as a source for clinical information.

In a related fashion, the American Medical Association suggested that readjustments must be made in medical education which shift the emphasis from the acquisition of information to the selection, organization and evaluation of information (23). Such a suggestion implies the need and importance for pharmacists to be involved as drug information specialists and clinical consultants (1). Bell et al. (24) and Hull et al. (25) have shown in their works that physicians will accept and use pharmacists as drug information specialists in patient care settings. Fisher and Pathak (26) indicated "that most recently graduated pharmacists are prepared to assume the role of drug information consultants." They also indicated that "one might postulate that strengthening of physician peer pressure could increase the use of pharmacists as a source of clinical drug information."

Drug Information Centers

The role of the pharmacist as a drug information specialist developed as an early example of the clinical responsibility of the pharmacy profession. The role was formalized with the development of drug information centers. The first drug information center in the United States was established in 1962 at the University of Kentucky by Burkholder (27). Today there are over 90 centers throughout the country employing over 200 fulltime and part-time pharmacists (7).

The needs and purpose of a drug information center were described by Francke in 1963 in "The Drug Information Center - A Professional Need and Opportunity" who wrote ". . .There is not the need so much for more drug information sources as there is for the organization and centralization of information now available and for an experienced and well-qualified

person to disseminate it. No individual physician can hope to maintain complete sources of drug information. But each can refer to a central source where he may obtain information on investigational drugs, drug reactions, availability of drugs, comparisons and contrasts of groups of drugs, incompatibilities, milliequivalents, reports on individuals drugs, and so forth." Francke suggested that the establishment of drug information centers by pharmacists familiar with the drug literature could adequately meet the drug information needs of physicians. By establishing drug information centers, a small number of pharmacists trained as drug information specialists could meet the needs of thousands of physicians serving millions of patients (28). As the concept of drug information specialists and centers evolved, the purposes and tasks of drug information centers became increasingly apparent. These purposes include:

1. Providing accurate, unbiased drug information (7);

2. Teaching students in medicine, dentistry, nursing, and pharmacy (29);

3. Providing health professionals with accurate drug information and answering drug-related questions (5);

4. Maintaining and updating the information base of the center (30, 31);

5. Acting as an information source to the public through lectures, presentations or patient counseling (7);

6. Providing services 24 hours a day, seven days a week (7);

7. Collecting and reporting adverse drug reactions (29).

Evaluation of Drug Information Services

Several investigators have evaluated and compared various drug

information services and systems. These studies have used various methods and criteria to quantitatively or qualitatively predict the value of the services for certain information needs. Yokel et al. compared four toxicology services (Poisindex, ToxiFile, Clinical Toxicology of Commercial Products and National Clearinghouse for Poison Control Centers). They determined the frequency of finding entries for substances known to be involved in accidental pediatric ingestions. They also evaluated the extent of the content and management information, and the time required to obtain the information for the four services. They found that Poisindex was more complete than the others. ToxiFile was more useful than the remaining two services, although the latter were judged useful in over 70 percent of accidental toxic ingestions by children (32).

Another study performed by Bell evaluated different drug interaction publications in the retrieval and application of drug interaction information. He indicated that the American Pharmaceutical Association's Evaluations of Drug Interactions and Hansten's Drug Interaction were the most comprehensive references. Stockley's Drug Interactions and Their Mechanism was considered nearly as complete. Cohen's Drug Interactions: A Handbook for Clinical Use, Gant's Drug Interactions Index: A Survey of Drug Interactions and Hartshorn's Handbook of Drug Interactions were deemed useful as an added check if an interaction suspected clinically was not included in any of the former groups (33).

Tourville and McLeod have compared the clinical utility of International Pharmaceutical Abstracts (I.P.A.), Iowa Drug Information Service (I.D.I.S.), and deHaen Drugs In Use and deHaen Drugs in Research by obtaining the number of references for questions in five different

clinical areas (general information on new drugs, comparative efficacy studies, adverse drug reactions, biopharmaceutics and pharmacokinetics), and the amount of time for each search. In their results they indicated that it was apparent that I.D.I.S. has the highest relative utility for obtaining clinical drug information. The two deHaen services provided broad coverage of the primary clinical literature, whereas I.P.A. was effective in locating many useful drug information references (34). Cluxton et al. compared quantitatively and qualitatively the usefulness of five information services in producing citations on the bioavailability of the oral dosage forms of five drugs. They indicated that I.D.I.S. and the deHaen service had the lowest number of citations with intermittent search time, MEDLINE was the most efficient service, I.P.A. had the highest percent of unique citations, and Index Medicus provided the highest number of citations but required more search time (35).

In 1973 Cardoni made a comparison of Current Contents' Life Sciences and Clinical Practice by determining the relative benefits derived from each service by hospital pharmacists. He concluded that the use of either service was an efficient and economical method of keeping abreast of the current literature of hospital and clinical pharmacy (36).

Madden and MacDonald quantitatively evaluated nine drug information services by obtaining the total number of citations for each of ten drugs, and the degree of overlap between those services used in the study. Their qualitative analysis was based upon the number of relevant references for three drugs and the degree of overlap. They indicated that with respect to computerized services, Excerpta Medica Drugdoc (EMD) provided the most comprehensive and complete coverage of the drug literature. Medlars complemented EMD and therefore should be used in combination.

Toxline was considered unsuitable. In the case of manual services, I.D.I.S. was the most comprehensive. However, a combination of I.D.I.S., Index Medicus and Drug Literature Index would provide the most comprehensive search. The deHaen Drugs In Use was found to be unsuitable (37).

Fortner et al. reviewed 100 abstracts of deHaen Drugs in Use service to determine the reliability of this drug information service. They concluded that the subscriber is urged to use the deHaen Drugs In Use abstracts as a means of literature access only, and not as a primary source of drug information due to the high error rate of abstracts (38). In 1978 Milne compared the usefulness of I.D.I.S. and MEDLINE in meeting the needs of a hospital-based drug information service and indicated that I.D.I.S. should be used since it provides the full article, while MEDLINE should be reserved for questions that cannot be answered by I.D.I.S. (39).

Oncology as a Developing Specialty in Pharmacy

The increasing use of antineoplastic agents has led to the necessity for pharmacists to specialize and to be responsible for these agents. In recent years clinical pharmacy services have been offered in oncology patient care areas. As a specialist, the oncology pharmacist started to provide many services to patients and physicians as described by See and Bergquist in 1976 (40) which include:

1. Drug Histories. The pharmacist can provide the physician with information about the patient's past and present medications, allergies, and side effects of antineoplastic agents.

2. Monitoring Drug Therapy. The pharmacist plays a role in monitoring drug therapy, e.g., cumulative drug toxicity, therapeutic incompatibility, drug interactions, liver and renal function, and calculation of

dosage. The pharmacist can also monitor chemotherapeutic agents' responses and toxicities.

3. Patient Drug Profiles. For each patient a drug profile can be prepared by the pharmacist. Data to be included in the profile include the patient history, laboratory data, past drug therapy, past progress notes, current therapy and patient response.

4. Drug Therapy Consultations. These drug consultations are important for cancer patients due to the severity of their conditions and the toxicities associated with their therapy. The patient should be counseled on side effects of the antineoplastic agents, drugs and food that may interact with his medications, his drug regimen, and any other changes that may occur during chemotherapy.

5. Coordination Between the Pharmacist and Physician. The physician who anticipates the treatment of a cancer patient may not be familiar with the patient's antineoplastic agents, especially their toxicities or pharmacological properties. The oncology pharmacist can provide drug information as needed. Additionally, the oncology pharmacist can help insure that the antineoplastic agents are available in local pharmacies and hospitals.

6. Drug Information Source. A special drug information problem exists with cancer chemotherapy due to the number of investigational chemotherapeutic agents in use. This problem can be solved by the oncology pharmacist serving as a source of drug information concerning the stability, toxicity, adverse effects, pharmacology, and dosing of the investigational and non-investigational antineoplastic agents. Additionally, all dosage calculations made by the physician may be checked by the pharmacist. Laboratory indices which include blood counts, bone marrow analysis

and liver and renal function tests, are used by the oncology pharmacist (41). Kitzman and Martinson reported in 1981 that more information about cancer chemotherapeutic agents was desired by patients. They concluded that pharmacists have filled an information gap by providing drug information to cancer patients and family members about a group of antineoplastic drugs that had been poorly understood by the public (42).

7. Inservice Education. The oncology pharmacist can provide education to professionals and patients about the administration, dosage, side effects, and any other new information regarding the antineoplastic agents. Blumer emphasized in her study that the education of pharmacists "must expand beyond drugs. It must include an indepth understanding of the disease state and care of the cancer patient in order to be of maximum benefit to the health care team" (43). In addition the oncology pharmacist can offer many services such as preparation of chemotherapy and coordination of its administration, and supervision of outpatient treatment facilities.

The oncology pharmacist can expand his service to include participation in clinical research and protocol development. He/she may participate in the clinical testing of investigational drugs and disseminate information on investigational drugs and protocols to the clinician, medical center staff, and community practitioners (44). Furthermore, a specially trained oncology pharmacist can assist the dietician in identifying patients' nutritional problems, recommending food supplements, and restructuring their diets to insure adequate nutrition (45). Kellick et al. wrote in their study that the addition of pharmacists to this area (oncology) would bring continuity and organization to the use of antineoplastic agents, decrease the length of time a patient must spend in

the hospital, and provide an important safeguard against medication errors (46).

A special medical oncology training program is offered by the University of Tennessee (47). The goal of this program is to prepare the oncology pharmacist for expanded services to oncology patients. These include instruction concerning the clinical application of antineoplastic agents, improved communication, and comprehensive cancer management. In addition to the treatment phase of cancer management, the oncology pharmacist may also contribute to other phases including etiology, prevention, detection, rehabilitation, and continuing care. These services may decrease morbidity and mortality in cancer patients in nonurban communities by improving the detection and treatment of cancer in its early stages.

Purpose of the Study

An increasing number of pharmacists are specializing in the treatment of cancer patients due to the increasing body of knowledge in oncology. Because of the growth of the drug literature related to oncology, this study is designed to determine the usefulness of three drug information services as a source of information on investigational antineoplastic agents. The study is designed to evaluate I.P.A., I.D.I.S., and deHaen Drugs In Use service quantitatively and qualitatively. No study has been published to date evaluating the utility of these three services as information sources for investigational antineoplastic agents. I.D.I.S. and deHaen Drugs In Use service are selected for evaluation because they are in common usage as clinical drug information services. I.P.A. is selected because it is the primary pharmaceutical abstracting service in the U.S.

If these three services are effective in providing general information concerning investigational cancer chemotherapeutic agents, it could prevent the necessity of using or purchasing additional, alternative, or more costly information services. Further, by determining which service is the most appropriate source of information on cancer chemotherapy, the pharmacist may be able to obtain information more efficiently.

Methodology

This study was designed to measure the comparative utility of three indexing and abstracting drug information services in providing data about antineoplastic agents. The three services studied were deHaen Drugs In Use, Iowa Drug Information Service (I.D.I.S.), and International Pharmaceutical Abstracts (I.P.A.).

Description of the Three Services

deHaen Drugs In Use (48,49). This service was established by Paul deHaen who started its publication in 1964 as one of three services. The other two services are: deHaen Drugs In Research and deHaen Drugs In Prospect. deHaen Drugs In Use reviews 1000 journals and abstracts about 7,500 articles. These abstracts are found on microfiche cards. Each abstract consists of information obtained from the original article, including number of patients in the study, study design, dosage, route of administration, special description related to the subject (e.g., age, sex, and the disease state), purpose of the study, adverse reactions, laboratory values and the author's comment and conclusion.

The annual subscription rate for deHaen Drugs In Use is $1095. An additional fee is charged for the computerized index that is available. The lag time, or time period from publication of the original article to the appearance of the abstract in deHaen Drugs In Use, is four to five months.

Iowa Drug Information Service (I.D.I.S.) (48,50). I.D.I.S. was developed by William Tester and initiated in 1966. This service reviews

156 journals per year and included 17,536 articles in 1980. These articles are related to drugs or drug therapy. The indexing information is printed in microfiche cards which are labeled and titled alphabetically by drug index terms or disease index terms. Other index terms are used in all index cards including: title, author, microfilm number, source, and special codes called clinical descriptors, which are used to describe or define the article of interest. The subscription cost is $900 per year and has a lag time of two to four months. However, I.D.I.S. has a unique feature in that it provides a microfiche copy of the original article.

International Pharmaceutical Abstracts (I.P.A.) (48,51). I.P.A. abstracts 5,000 articles per year. These articles appear in 600 journals related to pharmaceutical science and practice. There are about twenty-five sections in each issue on different topics concerning drug pharmaceutical properties such as formula and formulation, parenteral solutions, kinetics, adverse reactions, and drug evaluations. The first year of publication was 1964. Current subscription cost is $250 annually, and the service has a three to six months lag time. In 1970, I.P.A. computerized its service to provide additional information, including the citation, complete abstract, and index as a part of the Toxline service.

Table 1 summarizes the features of these three information services.

Quantitative Evaluation

The quantitative evaluation was based on determining the total number of citations for antineoplastic drugs in each service per year and obtaining the total number of citations for five selected investigational antineoplastic agents (Table 2) in each service per year for two years.

Table 1

Features of the Three Information Services

Name of the Service	First year of Publication	No. of Journals Abstracted/ Indexed	Cumulative No. of Articles Abstracted/ Indexed	Lag Time (Months)	Annual Subscription Cost
deHaen Drugs In Use	1964	1,000	7,500	4-5	$1,095
Iowa Drug Information Service (I.D.I.S.)	1966	156	17,536	2-4	$ 900
International Pharmaceutical Abstracts (I.P.A.)	1964	600	5,000	3-6	$ 250

Table 2

The Five Selected Investigational Antineoplastic Agents

Generic Name	Trade Name	Manufacturer
Amsacrine	--	Bristol
Etoposide	--	Bristol
Ifosfamide	Ifex	Mead Johnson
Teniposide	--	Bristol
Vindesine	Eldisine	Lilly

The period of quantitative evaluation was 1980 and 1981. The investigational antineoplastic agents studied were selected by the oncology pharmacy staff at the Veterans Administration Hospital, Palo Alto, California.

Qualitative Evaluation

This analysis was based on the ability of each service to give useful information related to the five antineoplastic agents previously described. These five antineoplastic agents are distributed by the National Cancer Institute (N.C.I.) and at the time of this study were classified as investigational agents by the Food and Drug Administration. Based upon the categories of questions commonly asked by the oncology medical staff at the V.A. hospital, several types of questions were designed and used to qualitatively evaluate the three services. These categories of questions are listed in Table 3.

The evaluation of each service and its ability to provide relevant drug information for each of the categories for each of the investigational agents was based solely on the abstract or index provided by each service. This method was used to test the ability of each service to give useful drug information from its abstract or index without reference to the primary literature. The first question used in this study was related to the dose of each agent, e.g., how many µg or mg should be used in treatment, and the frequency of administration. The second question was related to the ability of these services to provide information about the route of administration of the agents. The third question was designed to address the problem of side effects or adverse reactions to the investigational agents. In the fourth question citations were sought

Table 3

The Seven Categories of Questions
Used in Qualitative Analysis

1. What is the dose of the antineoplastic agent?
2. What is the route of administration?
3. What are the side effects or adverse reactions?
4. What is the mechanism of action?
5. What is the pharmacokinetics?
6. Is the agent used alone?
7. Is the agent used in combination with other drugs?

related to the mechanism of action of each agent, including mechanism of action *in vitro*, *in vivo* or in human studies. The fifth type of question concerned the pharmacokinetics for each agent, including metabolism, absorption, distribution, excretion, and half-life in animals or humans. The last two questions were related to the use of each agent alone or in combination with other drugs or treatment, e.g., radiotherapy.

The method of identifying the citations related to the categories of the questions was based upon the unique design and the characteristics of each of the services. For example, to obtain the available citations for the seven questions using deHaen Drugs In Use service, the proprietary name index, therapeutic classification index and data cards from January to December, 1980 and 1981 were examined. In I.D.I.S. the microfiche headers and the index frame of each microfiche were used to locate the drug or disease index term desired for 1980 and 1981. In contrast, the source of information from I.P.A. was the abstracts from January to December for each year.

Several search terms were used for each agent in this study. These search terms included the generic name of the agent and its synonyms. These terms were used to gain access to relevant citations in each service and are listed in Table 4.

Quantitative Analysis of Data

The number of citations for antineoplastics agents was totaled for each service in 1980 and 1981 and compared using a modification of the methods of Tourville and McLeod (34). Their method includes calculating the mean based upon the total number of citations in each service evaluated. To analyze the data in the present study, comparisons were made

Table 4

Search Terms

1.	Amsa:	1. Amsa 2. Amsacrine 3. Acridinylamine-anisidide and aniside 4. M-Amsa 5. NSC-249992
2.	Etoposide:	1. E toposide 2. Epipodophyllotoxin 3. Vp - 16 4. NSC-141540
3.	Ifosfamide:	1. Ifosfamide 2. Isophosphamide 3. Iso-endoxin 4. Asta-4942 5. Z-4942 6. NSC-109724
4.	Teniposide:	1. Teniposide 2. Vm-26
5.	Vindesine:	

using a relative data locating index to determine the mean by which the services can be compared. The relative data locating index was calculated by dividing the greatest number of citations of any service into the number of ditations from the service studied and multiplying by 100:

$$\text{Relative data locating index} = \frac{\text{No. of citations of service studied}}{\text{Greatest No. of citations of any service}} \times 100$$

Qualitative Analysis of Data

Qualitative analysis was based on the ability of each service to provide useful information related to seven questions about five antineoplastic agents. The total number of the answers (citations) was collected for each agent in each service. A nonparametric test, "Friedman Two-Way Analysis of Variance by Ranks," was used to determine if the number of citations differed significantly. The Friedman test converts each subject's scores to ranks. Then the sum of each column is obtained. By using Friedman's formula: $\chi_r^2 = \frac{12}{nk(k+1)} (\Sigma R^2) - 3n (k+1)$

where:

k = the number of columns

n = the number of subjects

R^2 = squared sum of column ranks

χ_r^2 value can tell whether or not there is a significant difference among ranks (52,53). If this value has a probability of 0.05 or less, (when k = 3 and n = 5, χ_r^2 has a critical value of 6.4) a post-hoc test may be used to determine which of the three services differs significantly from the other (54). In this test, a pair-wise difference is significant if the interval bounded by $\hat{\Psi} \pm \sqrt{\chi_r^2 \text{ Var } (\hat{\Psi})}$ does not contain "0" where:

$$\hat{\Psi} = \Sigma a_k \overline{R}_k$$

and

$$\text{Var } (\hat{\Psi}) = \frac{k\ (k+1)}{12\ n} \quad \Sigma a_k^2$$

For all pair wise comparisons a_k is the coefficient of the comparison and $\overline{R}_k$ is the average rank.

Results

The results of the quantitative analysis of the three services, deHaen Drugs In Use, Iowa Drug Information Service, and International Pharmaceutical Abstracts, are shown in Tables 5-7.

Table 5 shows the total number of antineoplastic citations in each service. In 1980 deHaen Drugs In Use yielded 1304 citations, while I.D.I.S. and I.P.A. provided 436 and 347, respectively. In 1981, these three services provided 1400, 433, 427 antineoplastic citations for deHaen Drugs In Use, I.D.I.S., and I.P.A., respectively. Table 6 shows that the total number of citations in 1980 for the five selected investigational antineoplastic agents were: 45 in the deHaen service, 83 in I.D.I.S., and 5 in I.P.A. In 1981 deHaen provided 73 citations; I.D.I.S. 115; and I.P.A. provided only 7 citations (see Table 7).

The results of the qualitative analysis of the three services are shows in Tables 8, 9 and 10 where the total number of citations related to the seven questions for the five agents was obtained in 1980 and 1981. Statistical analysis of the data was done by two tests. The first test was the Friedman Two-Way Analysis of Variance by Ranks, which was used to determine if these three services were significantly different from each other. When this test was applied, it was found that the three services were significantly different ($P < 0.05$) in obtaining citations for the questions related to dose, route of administration, adverse reactions and single therapy in 1980 and 1981 (see Tables 11-16, 22). It was found that these three services were significantly different ($P < 0.05$) in

obtaining information in 1981 about the agent when used in combination with other agents (see Table 24). However, there was no difference ($P > 0.05$) between these three services in 1980 and 1981 in obtaining citations concerning mechanism of action (see Tables 17, 18) and pharmacokinetics (see Tables 19, 20). In addition, there was no difference ($P > 0.05$) in obtaining information about the agents studied in combination with other agents in 1980.

The second test was the post-hoc test which was applied to the data in those instances where there was a demonstrated significant difference between the three services. The post-hoc test was used to determine, through pairwise comparison, which service was significantly different ($P < 0.05$) from the other. These results are listed in Tables 11-16, 21, 22, 24. In addition, Table 11 includes the sequence of calculations associated with the Friedman and post-hoc analysis.

It was found that I.D.I.S. was significantly different ($P < 0.05$) from I.P.A. in obtaining citations in 1980 concerning dose, route of administration and adverse reactions of the five investigational antineoplastic agents. There was no significant difference ($P > 0.05$) between I.D.I.S. and the deHaen service or between deHaen service and I.P.A. for questions about dose, route of administration and adverse reactions in 1980. In addition, it was found that there was no significant difference ($P > 0.05$) between these three services in providing information related to mechanism of action, pharmacokinetics, single or combination therapy questions in 1980. In 1981 it was found that I.D.I.S. was significantly different ($P < 0.05$) from I.P.A. for questions related to route of administration, adverse reactions, and use of the agents alone. There was no significant difference ($P > 0.05$) between I.D.I.S. and the deHaen

service or between the deHaen service and I.P.A. for questions regarding route of administration, adverse reactions, and use of the agents alone. However, there was no significant difference ($P > 0.05$) between these three services in obtaining information related to dose, mechanism of action, pharmacokinetics and use of the agents in combination with other antineoplastic agents in 1981.

Table 5

Total Number of Citations for Antineoplastic Agents in Each Service in 1980 and 1981

	deHaen Drugs In Use	I.D.I.S.	I.P.A.
Total number of citations in 1980	1304	436	347
Relative data locating index, 1980	100	33.4	26.6
Total number of citations in 1981	1400	433	427
Relative data locating index, 1981	100	30.9	30.5

Table 6

Number of Citations for the Five Agents in the Three Services in 1980

Drug Name	No. of Citations in deHaen Drugs in Use	No. of Citations in I.D.I.S.	No. of Citations in I.P.A.
1. Amsacrine	9	10	1
2. Etoposide	10	33	2
3. Ifosfamide	3	8	1
4. Teniposide	6	17	-
5. Vindesine	17	15	1
Total	45	83	5
Relative data locating index	54	100	6

Table 7

Number of Citations for the Five Agents in the Three Services in 1981

Drug Name	No. of Citations in deHaen Drugs in Use	No. of Citations in I.D.I.S.	No. of Citations in I.P.A.
1. Amsacrine	18	24	2
2. Etoposide	14	45	3
3. Ifosfamide	10	12	1
4. Teniposide	9	9	1
5. Vindesine	22	25	-
Total	73	115	7
Relative data locating index	63	100	6

Table 8

Number of Citations for the Seven Questions about the Five Agents in deHaen Drugs In Use for 1980 and 1981

Category of Question	Number of Retrieved Citations By Year for Each Agent											
	Amsacrine		Etoposide		Ifosfamide		Teniposide		Vindesine		Total[a]	
	1980	1981	1980	1981	1980	1981	1980	1981	1980	1981	1980	1981
Dose	8	16	9	14	1	10	5	8	16	21	39	69
Route of Administration	6	14	7	13	2	9	3	6	12	21	30	63
Adverse Reactions	8	17	7	13	1	9	5	6	10	13	31	58
Mechanism of Action	-	-	-	-	1	-	-	-	1	-	2	-
Pharmacokinetics	1	1	1	1	1	1	-	1	1	3	4	7
Alone	9	17	6	6	1	3	3	3	15	15	34	44
Combination	-	1	4	.8	2	7	3	6	2	7	11	29
Total Number of Citations Retrieved	9	18	10	14	3	10	6	9	17	22		

[a]Refers to the total number of citations related to each question for the five agents.

Table 9

Number of Citations for the Seven Questions about the Five Agents in Iowa Drug Information Service for 1980 and 1981

Category of Question	Number of Retrieved Citations By Year for Each Agent											
	Amsacrine		Etoposide		Ifosfamide		Teniposide		Vindesine		Total[a]	
	1980	1981	1980	1981	1980	1981	1980	1981	1980	1981	1980	1981
Dose	9	21	25	26	5	6	14	7	11	22	64	82
Route of Administration	9	15	23	22	5	6	14	6	10	24	66	73
Adverse Reactions	9	20	22	29	8	9	14	8	14	21	67	87
Mechanism of Action	-	1	-	1	2	-	1	-	2	1	5	3
Pharmacokinetics	2	1	2	1	-	1	2	1	1	1	7	5
Alone	2	22	8	5	3	6	7	6	12	18	32	57
Combination	8	2	28	40	5	6	10	3	3	7	54	58
Total Number of Citations Retrieved	10	24	33	45	8	12	17	9	15	25		

[a]Refers to the total number of citations related to each question for the five agents.

Table 10

Number of Citations for the Seven Questions About the Five Agents in International Pharmaceutical Abstracts for 1980 and 1981

Category of Question	Number of Retrieved Citations By Year for Each Agent											
	Amsacrine		Etoposide		Ifosfamide		Teniposide		Vindesine		Total[a]	
	1980	1981	1980	1981	1980	1981	1980	1981	1980	1981	1980	1981
Dose	1	2	-	-	1	1	-	-	1	-	3	3
Route of Administration	-	1	-	-	-	-	-	-	-	-	-	1
Adverse Reaction	1	2	-	-	1	1	-	1	1	-	3	4
Mechanism of Action	-	-	-	-	1	-	-	-	1	-	2	-
Pharmacokinetics	1	1	1	1	-	1	-	-	-	-	2	3
Alone	1	2	-	1	1	-	-	1	1	-	3	4
Combination	-	-	2	2	-	1	-	-	-	-	2	3
Total Number of Citations Retrieved	1	2	2	3	1	1	-	1	1	-		

[a]Refers to the total number of citations related to each question for the five agents.

Table 11

Ranking the Three Services by Number of Citations
Related to Dose for Each Agent in 1980

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	8	(2)	9	(3)	1	(1)
2. Etoposide	9	(2)	25	(3)	-	(1)
3. Ifosfamide	1	(1.5)	5	(3)	1	(1.5)
4. Teniposide	5	(2)	14	(3)	-	(1)
5. Vindesine	16	(3)	11	(2)	1	(1)
Σ =	39	(10.5)	64	(14)	3	(5.5)

a = deHaen Drugs in Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

(see page 39 for statistical analysis)

Dose - 1980

	T_1	T_2	T_3
ΣR_k	10.5	14	5.5
$\frac{\Sigma R_k}{R_k}$	10.5/5 = 2.1	2.8	1.1

- Friedman test:

$$\chi_r^2 = \left| \frac{12}{nK\,(K+1)} \right| (\Sigma R_k^2) - 3n\,(K+1)$$

$$= \frac{12}{5.3.4} \quad (10.5^2 + 14^2 + 5.5^2) - 3.5.4$$

$$= \quad 0.2 \quad (336.5) \quad - \quad 60$$

$$= \quad 67.3 \quad - \quad 60 \quad = \quad 7.3 \text{ has probability} < 0.05$$

- Post-Hoc test:

$$T_1 - T_2$$

$$\hat{\Psi} = +1\,(2.1) - 1\,(2.8) = -0.7$$

$$\text{var}\ (\hat{\Psi}) = \frac{k\,(k+1)}{12\,n} \Sigma\, \alpha_k^2$$

$$= \frac{3 \cdot 4}{12 \cdot 5} \quad (1^2 + (-1)^2$$

$$= \frac{12}{60} \cdot 2 \quad = 0.4$$

$$\text{Test} = -0.7 \pm \sqrt{6.2^{*}(0.4)} = -0.7 \pm 1.6$$

$$= -0.7 \pm 1.6 = -2.3 \text{ to } 0.9 \text{ Contain "0", Not significant}$$

$$T_1 - T_3$$

$$\hat{\Psi} = 1$$

$$\text{Test} = 1 \pm 1.6 = -0.6 \text{ to } 2.6 \text{ Contain "0" - Not significant}$$

$$T_2 - T_3$$

$$\hat{\Psi} = 1.7$$

$$\text{Test} = 1.7 \pm 1.6 = 0.1 \text{ to } 3.3 \text{ Does not contain "0" significant at } P < 0.05.$$

* Value from table N of K = 3, N = 5 at 0.05 level

Table 12

Ranking the Three Services by Number of Citations Related to Dose for Each Agent in 1981

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	16	(2)	21	(3)	2	(1)
2. Etoposide	14	(2)	26	(3)	-	(1)
3. Ifosfamide	10	(3)	6	(2)	1	(1)
4. Teniposide	8	(3)	7	(2)	-	(1)
5. Vindesine	21	(2)	22	(3)	-	(1)
Σ =	69	(12)	82	(13)	3	(5)

- Friedman test: $\chi_r^2 = 7.6$ has $P < 0.05$
- Post-hoc test: $T_1 - T_2$ No significant difference
  $T_1 - T_3$ No significant difference
  $T_2 - T_3$ No significant difference

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 13

Ranking the Three Services by Number of Citations Related to Route of Administration for Each Agent in 1980

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	6	(2)	9	(3)	-	(1)
2. Etoposide	7	(2)	23	(3)	-	(1)
3. Ifosfamide	2	(2)	5	(3)	-	(1)
4. Teniposide	3	(2)	14	(3)	-	(1)
5. Vindesine	12	(3)	10	(2)	-	(1)
Σ =	30	(11)	61	(14)	0	(5)

- Friedman test: $\chi_r^2 = 8.4$ has $P < 0.05$
- Post-hoc test: $T_1 - T_2$ No significant difference
  $T_1 - T_3$ No significant difference
  $T_2 - T_3$ Significant difference ($P < 0.05$)

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 14

Ranking the Three Services by Number of Citations Related to Route of Administration for Each Agent in 1981

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	14	(2)	15	(3)	1	(1)
2. Etoposide	13	(2)	22	(3)	-	(1)
3. Ifosfamide	9	(3)	6	(2)	-	(1)
4. Teniposide	6	(2.5)	6	(2.5)	-	(1)
5. Vindesine	21	(2)	24	(3)	-	(1)
Σ =	63	(11.5)	73	(13.5)	1	(5)

- Friedman test: $\chi_r^2 = 7.9$ has $P < 0.05$
- Post-hoc test: $T_1 - T_2$ No significant difference
  $T_1 - T_3$ No significant difference
  $T_2 - T_3$ Significant difference ($P < 0.05$)

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 15

Ranking the Three Services by Number of Citations Related to Adverse Reactions for Each Agent in 1980

Investigational Agents	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	8	(2)	9	(3)	1	(1)
2. Etoposide	7	(2)	22	(3)	-	(1)
3. Ifosfamide	1	(1.5)	8	(3)	1	(1.5)
4. Teniposide	5	(2)	14	(3)	-	(1)
5. Vindesine	10	(2)	14	(3)	1	(1)
Σ =	31	(9.5)	67	(15)	3	(5.5)

- Friedman test: $\chi_r^2 = 9.1$ has $P < 0.05$
- Post-hoc test: $T_1 - T_2$ No significant difference
  $T_1 - T_3$ No significant difference
  $T_2 - T_3$ Significant difference ($P < 0.05$)

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d - Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 16

Ranking the Three Services by Number of Citations Related to Adverse Reactions for Each Agent in 1981

Investigational Agents	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	17	(2)	20	(3)	2	(1)
2. Etoposide	13	(2)	29	(3)	-	(1)
3. Ifosfamide	9	(2.5)	9	(2.5)	1	(1)
4. Teniposide	6	(2)	8	(3)	1	(1)
5. Vindesine	13	(2)	21	(3)	-	(1)
Σ =	38	(10.5)	87	(14.5)	4	(5)

- Friedman test: $\chi_r^2 = 9.1$ has $P < 0.05$
- Post-hoc test: $T_1 - T_2$ No significant difference
  $T_1 - T_3$ No significant difference
  $T_2 - T_3$ Significant difference ($P < 0.05$)

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 17

Ranking the Three Services by Number of Citations Related to Mechanism of Action for Each Agent in 1980

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	-	(2)	-	(2)	-	(2)
2. Etoposide	-	(2)	-	(2)	-	(2)
3. Ifosfamide	1	(1.5)	2	(3)	1	(1.5)
4. Teniposide	-	(1.5)	1	(3)	-	(1.5)
5. Vindesine	1	(1.5)	2	(3)	1	(1.5)
Σ =	2	(8.5)	5	(13)	2	(8.5)

- Friedman test $\chi_r^2 = 2.7$ has $P > 0.05$

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 18

Ranking the Three Services by Number of Citations Related to Mechanism of Action for Each Agent in 1981

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	-	(1.5)	1	(3)	-	(1.5)
2. Etoposide	-	(1.5)	1	(3)	-	(1.5)
3. Ifosfamide	-	(2)	-	(2)	-	(2)
4. Teniposide	-	(2)	-	(2)	-	(2)
5. Vindesine	-	(1.5)	1	(3)	-	(1.5)
Σ =	0	(8.5)	3	(13)	0	(8.5)

- Friedman test $\chi^2_r = 2.7$ has $P > 0.05$

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 19

Ranking the Three Services by Number of Citations Related to Pharmacokinetics for Each Agent in 1980

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	1	(1.5)	2	(3)	1	(1.5)
2. Etoposide	1	(1.5)	2	(3)	1	(1.5)
3. Ifosfamide	1	(3)	-	(1.5)	-	(1.5)
4. Teniposide	-	(1.5)	2	(3)	-	(1.5)
5. Vindesine	1	(2.5)	1	(2.5)	-	(1)
Σ =	4	(10)	7	(13)	2	(7)

- Friedman test: $\chi_r^2 = 3.6$ has $P > 0.05$

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 20

Ranking the Three Services by Number of Citations Related to Pharmacokinetics for Each Agent in 1981

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	1	(2)	1	(2)	1	(2)
2. Etoposide	1	(2)	1	(2)	1	(2)
3. Ifosfamide	1	(2)	1	(2)	1	(2)
4. Teniposide	1	(2.5	1	(2.5)	-	(1)
5. Vindesine	3	(3)	1	(2)	-	(1)
Σ =	7	(11.5)	5	(10.5)	3	(8)

- Friedman test: $\chi_r^2 = 1.3$ has $P > 0.05$

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 21

Ranking the Three Services by Number of Citations Related to Single Therapy for Each Agent in 1980

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	9	(3)	2	(2)	1	(1)
2. Etoposide	6	(2)	8	(3)	-	(1)
3. Ifosfamide	1	(1.5)	3	(3)	1	(1.5)
4. Teniposide	3	(2)	7	(3)	-	(1)
5. Vindesine	15	(3)	12	(2)	1	(1)
Σ =	34	(11.5)	32	(13)	3	(5.5)

- Friedman test: $\chi_r^2 = 6.3$ has $P < 0.05$
- Post-Hoc test: $T_1 - T_2$ No significant difference
  $T_1 - T_3$ No significant difference
  $T_2 - T_3$ No significant difference

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 22

Ranking the Three Services by Number of Citations Related to Single Therapy for Each Agent in 1981

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	17	(2)	22	(3)	2	(1)
2. Etoposide	6	(3)	5	(2)	1	(1)
3. Ifosfamide	3	(2)	6	(3)	-	(1)
4. Teniposide	3	(2)	6	(3)	1	(1)
5. Vindesine	15	(2)	18	(3)	-	(1)
Σ	44	(11)	57	(14)	4	(5)

- Friedman test: $\chi_r^2 = 8.4$ has $P < 0.05$
- Post-hoc test: $T_1 - T_2$ No significant difference
  $T_1 - T_3$ No significant difference
  $T_2 - T_3$ Significant difference ($P < 0.05$)

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 23

Ranking the Three Services by Number of Citations Related to Combination Therapy for Each Agent in 1980

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	-	(1.5)	8	(2)	-	(1.5)
2. Etoposide	4	(2)	25	(3)	2	(1)
3. Ifosfamide	2	(2)	5	(3)	-	(1)
4. Teniposide	3	(2)	10	(3)	-	(1)
5. Vindesine	2	(2)	3	(3)	-	(1)
Σ =	11	(9.5)	51	(14)	2	(5.5)

- Friedman test: $\chi_r^2 = 3.3$ has $P > 0.05$

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 24

Ranking the Three Services by Number of Citations Related to Combination Therapy for Each Agent in 1981

Investigational Agent	T_1[a]		T_2[b]		T_3[c]	
1. Amsacrine[d]	1	(2)	2	(3)	-	(1)
2. Etoposide	8	(2)	40	(3)	2	(1)
3. Ifosfamide	7	(3)	6	(2)	1	(1)
4. Teniposide	6	(3)	3	(2)	-	(1)
5. Vindesine	7	(2.5)	7	(2.5)	-	(1)
Σ =	29	(12.5)	58	(12.5)	3	(5)

- Friedman test: $\chi_r^2 = 7.5$ has $P < 0.05$
- Post-hoc test: $T_1 - T_2$ No significant difference
  $T_1 - T_3$ No significant difference
  $T_2 - T_3$ No significant difference

a = deHaen Drugs In Use Service
b = Iowa Drug Information Service
c = International Pharmaceutical Abstracts
d = Values in each column are the numbers of citations with the rankings listed in parenthesis.

Table 25

Summary of the Statistical Analysis of the Qualitative Evaluation

Category of Question	Significance, Friedman Test		Significance, χ_r^2	
	1980	1981	1980	1981
Dose	P < 0.05	P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P < 0.05 deHaen vs. I.P.A. P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P > 0.05 deHaen vs. I.P.A. P > 0.05
Route of Administration	P < 0.05	P < 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P < 0.05 deHaen vs. I.P.A. P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P < 0.05 deHaen vs. I.P.A. P > 0.05
Adverse Reactions	P < 0.05	P < 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P < 0.05 deHaen vs. I.P.A. P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P < 0.05 deHaen vs. I.P.A. P > 0.05
Mechanism of Action	P > 0.05	P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P > 0.05 deHaen vs. I.P.A. P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P > 0.05 deHaen vs. I.P.A. P > 0.05
Pharmaco-kinetics	P > 0.05	P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P > 0.05 deHaen vs. I.P.A. P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P > 0.05 deHaen vs. I.P.A. P > 0.05
Alone	P < 0.05	P < 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P > 0.05 deHaen vs. I.P.A. P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P < 0.05 deHaen vs. I.P.A. P > 0.05
Combination	P > 0.05	P < 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P > 0.05 deHaen vs. I.P.A. P > 0.05	I.D.I.S. vs. deHaen P > 0.05 I.D.I.S. vs. I.P.A. P > 0.05 deHaen vs. I.P.A. P > 0.05

Discussion

This study used the abstract and index information of the three services as the principal means of evaluating and comparing them. For the quantitative analysis of these three services as a source of information concerning antineoplastic agents, the overall total number of citations is shown in Table 5. deHaen Drugs In Use service was found to provide the highest number of citations in both 1980 and 1981. By using relative data locating index in this analysis which is calculated as:

$$\text{Relative data locating index} = \frac{\text{No. of citations of service studies}}{\text{Greatest No. of citations of any service}} \times 100$$

I.D.I.S. provided 436 citations (relative data locating index = 33.4) in 1980, and 433 citations (relative data locating index = 30.9) in 1981. I.P.A. had 347 citations (relative data locating index = 26.6) for 1980, and almost the same relative data locating index, 30.5, in 1981 as I.D.I.S. deHaen Drugs In Use service had about three times the number of citations as I.D.I.S. or I.P.A. in 1980 and more than three times than either in 1981. This impressive difference in the total number of antineoplastic agents citations may be due to the difference in the number of journals which have been abstracted or indexed by each service. The deHaen service abstracts 1000 journals, I.P.A., 600 journals, while I.D.I.S. indexes only 156 journals. It should be mentioned that these numbers of citations as shown in Table 5 represented all citations that have been found in each service in each year, even though each citation may be listed more than once due to cross-indexing. It was beyond the scope of this project

to devise a method to eliminate replicate listings of the same citations.

Quantitative analysis of the data obtained from each service shows that there is a significant difference ($P < 0.05$) between these three services in the total number of references for these five agents. I.P.A. provided a limited number of reference citations when compared with I.D.I.S. or the deHaen service. Table 6 shows that in 1980 the total number of citations for the five investigational antineoplastic agents was 83 in I.D.I.S., 45 in the deHaen service (relative data locating index = 54), and only 5 citations in I.P.A. (relative data locating index = 6). In 1981, I.P.A. had 7 citations for the five investigational antineoplastic agents (relative data locating index = 6), while the deHaen service provided 73 citations (relative data locating index = 63), and I.D.I.S. contained 115 (see Table 7).

The qualitative evaluation of these three services was based on the ability of each service to provide useful therapeutic information related to the five selected investigational antineoplastic agents. Basic therapeutic information such as the dose, route of administration, and adverse reactions are important to the health care professionals as well as the patient. The pharmacist as a source of drug information and as a dispenser of the medications should be well informed concerning such information. In addition, the availability of a drug information service would be an excellent source of information for the pharmacist and other health care providers. It has been suggested that physicians and nurses do not provide the patients with adequate instructions related to their medication (13,55); and the patients do not want to waste the physician's time by questioning him about their medications (13). Leary et al.

reported that only 8.3 percent of patients in their study indicated that their physicians and nurses had explained their medication to them, even though 83.5 percent of the patients were suspected to be in danger due to problems related to self-administration of their medication at home (55). Furthermore, since non-prescription drugs for self-medication provide little information about their side effects, interaction with food or other drugs, and their dangers of use, access to drug information source would be helpful (56).

Based upon the need for therapeutic information about antineoplastic agents this study evaluated these three services according to the number of reference citations provided by each service in response to seven questions related to each agent. Tables 11 and 12 show that with respect to dose, I.D.I.S. was the best source of information in both 1980 and 1981, providing 64 and 82 citations respectively. The deHaen service had 39 citations in 1980 and 69 citations in 1981. I.P.A. was the lowest, providing 3 citations in each of 1980 and 1981. I.D.I.S. provided the highest number of citations regarding the route of administration in 1980 and 1981, 61 and 73 citations respectively. The deHaen service provided 30 and 63 citations in 1980 and 1981 respectively, while I.P.A. had no citations in 1980, and provided only one citation in 1981. There were more adverse reactions citations for the five investigational antineoplastic agents in I.D.I.S. than deHaen service or I.P.A. Tables 15 and 16 show that I.D.I.S. provided the highest number of citations. The deHaen service provided 31 and 58, while I.P.A. had 3 and 4 for 1980 and 1981, respectively. The pharmacokinetics and mechanism of action questions had the lowest total number of citations in each service in each year. As shown in Tables 19 and 20, for 1980 and 1981, I.D.I.S.

provided 7 and 5, the deHaen service provided 4 and 7, and I.P.A. had 2 and 3, respectively, for the pharmacokinetic question. For the mechanism of action question, the total number of citations in I.D.I.S. was 5 and 3, in the deHaen service 2 and 0, and in I.P.A. 2 and 0 for 1980 and 1981, respectively (see Tables 17 and 18). This finding can be explained by the fact that the five agents are still under investigation, and there were no studies completed regarding their effects in certain cases of cancer diseases. Information about the five investigational antineoplastic agents when studied in combination with other agents or alone is shown in Tables 21-24. It appeared that in both 1980 and 1981, the deHaen service and I.P.A. provided fewer citations related to combination therapy than for use of the agents alone. I.D.I.S. contained the highest number of citations for the agents studied in combination in 1980 and 1981.

Friedman Two-Way Analysis of Variance by Ranks test was applied to the data in this study to determine if these three services were significantly different in the total number of citations for each of the seven questions for each agent. If there was a significant difference, the Post-hoc test was then applied, providing a pairwise comparison of the three services. With respect to the question about dose, Table 11 shows that there was a significant difference ($P < 0.05$) between I.D.I.S. and I.P.A., but no significant difference ($P > 0.05$) between the deHaen service and I.P.A. or I.D.I.S. in 1980. In 1981 there was no significant difference ($P > 0.05$) between these three services. However, there was a significant difference ($P < 0.05$) between I.D.I.S. and I.P.A. in obtaining information related to the route of administration in both 1980 and 1981 as shown in Tables 13 and 14. There was no significant difference

($P > 0.05$) between the deHaen service and I.D.I.S. or I.P.A. during 1980 and 1981 for this question. There were similar statistical results for the three services concerning the adverse reactions question in 1980 and 1981 (Tables 15 and 16). In addition, Tables 19 and 20 show that there was no significant difference ($P > 0.05$) between the three services regarding pharmacokinetics and mechanism of action of the five investigational antineoplastic agents in 1980 and 1981. In the case of studies which have been done related to the five agents used alone or in combination with other agents, there were no significant differences ($P > 0.05$) between these three services in 1980. In 1981 there was a significant difference ($P < 0.05$) between I.D.I.S. and I.P.A. and no significant difference ($P > 0.05$) between the deHaen service and I.D.I.S. or I.P.A. (Tables 21-24).

These data and statistical analyses show the superiority of I.D.I.S in obtaining information related to the selected five investigational agents studied. This finding is related to the special orientation of each service of these three services. I.D.I.S. concentrates on drug and drug therapy information, while the deHaen service focuses on the therapeutic use and efficacy, clinical pharmacology, and toxicology of single drugs, and I.P.A. provides abstracts of information related primarily to the traditional pharmaceutical sciences.

These findings of data and statistical analyses are similar to those of Tourville and McLeod (34) who compared these three services by using clinical questions related to different clinical areas such as biopharmaceutics and toxicology, and indicated that I.D.I.S. has the highest relative utility for providing clinical drug information. Similar results were reported by Madden and MacDonald who evaluated and compared nine

drug information retrieval services (37), and found that I.D.I.S. was the most comprehensive manual service. I.D.I.S. provides a copy of the original article on microfiche which makes it more convenient for the user by not having to waste time searching for the original article in the literature. deHaen Drugs In Use provided good information concerning the five investigational antineoplastic agents. It was surprising, however, that there was no significant statistical difference between it and I.P.A., even though it had a higher total number of citations than I.P.A. for the antineoplastic agents and also for the selected five agents. These findings about the deHaen Drugs In Use service were similar to that of Tourville and McLeod who indicated that the deHaen service offered broad coverage of primary clinical literature. The results were different from that of Madden and MacDonald who concluded that the deHaen service was unsuitable. I.P.A. was found to be of little value in providing information related to the five investigational antineoplastic agents.

Summary and Conclusion

The need for drug information is increasing at a rapid rate. The pharmacist is fulfilling a role as a drug information specialist by providing information to the physician, nurse, patient, and others. The establishment of clinically oriented drug information centers has increased significantly since 1962 when the first drug information center was established.

The clinical pharmacist as a specialist in oncology offers his services to the physician and patient by providing information related to approved and investigational chemotherapeutic agents, monitoring drug therapy, calculating the dosage, providing laboratory indices, and monitoring responses and toxicities. The clinical pharmacist can conduct drug therapy consultations with patients by explaining the toxicities of their medication, side effects, and the use of this medication. He also can be a drug information source related to cancer chemotherapeutic agents, their pharmacology, adverse reactions, dosing, toxicities, etc.

Many studies have evaluated various drug information services, using methods and criteria to predict the value of the services for certain drug information needs. No published study has evaluated the usefulness of drug information services as a source for investigational antineoplastic agents. This present study was designed to compare deHaen Drugs In Use service, Iowa Drug Information Service (I.D.I.S.) and International Pharmaceutical Abstracts (I.P.A.) as a source of information on investigational cancer chemotherapeutic agents. Quantitative and qualitative methods were used to compare and evaluate these three

services. The relative data locating index for each service was used in the quantitative analysis in 1980 and 1981. Data show that there was a difference between the three services based upon the relative data locating index in 1980 and 1981 for all antineoplastic agents as well as the selected five investigational antineoplastic agents.

Two statistical tests were used to analyze the qualitative data. The first was the Friedman Two-Way Analysis of Variance by Ranks test which was used to determine whether or not a significant difference existed between the three services in providing information related to each question. If there was a significant difference, a post-hoc test was then applied to determine which one of the three services was significantly different from the others. The two tests (Friedman and post-hoc analysis) showed that I.D.I.S. was significantly different from I.P.A. in both 1980 and 1981, whereas there was no significant difference between deHaen Drugs In Use service and I.D.I.S. or I.P.A. in both 1980 and 1981.

Based on:

1. The quantitative analysis, which indicated that I.D.I.S. provided the highest number of citations regarding the five investigational antineoplastic agents;

2. The qualitative analysis, which also indicated that I.D.I.S. was significantly better than I.P.A. ($P < 0.05$);

3. The unique feature of I.D.I.S. in providing the full original article in its microfiche; and

4. The lower costs of I.D.I.S. ($900) when compared to the deHaen service ($1095),

it it concluded that I.D.I.S. is more comprehensive and appropriate than

the deHaen service or I.P.A. in obtaining information related to investigational antineoplastic agents.

Because of the relatively large number of citations contained in the deHaen Drugs In Use service, it is recommended as a useful second choice in obtaining therapeutic information about the antineoplastic agents. I.P.A. was found to be unsuitable as a source of information on investigational chemotherapeutic agents.

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