EVALUATION OF ADVERSE
DRUG REACTION REPORTING SYSTEMS

by

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A project submitted to the faculty of the

University of Utah in partial fulfillment of the requirements

for the degree of

Doctor of Pharmacy

College of Pharmacy

University of Utah

June 1984

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of James Barrett Nightingale in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

6/19/84
Date

Chairman, Supervisory Committee

Approved for the Department of Pharmacy Practice

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

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We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

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INTRODUCTION

In July 1979, in accordance with the Joint Commission on Accreditation of Hospitals (JCAH) standards, the Pharmacy and Therapeutics Committee approved a policy for reporting adverse drug reactions (ADRs) occurring within the 370-bed University of Utah Hospital. This policy was intended "to provide a mechanism to accurately and completely report adverse drug reactions which are suspected within the hospital". It required the health care provider initially suspecting the adverse drug reaction to complete an Adverse Drug Reaction Experience Report Form (Food and Drug Administration Form #1639). These report forms were to be available at each inpatient unit and outpatient clinic. The completed form was to be left in the pharmacy medication order box or taken directly to the pharmacy. In turn, all pharmacy personnel were to immediately forward the Adverse Drug Experience Report to the Drug Information Center. A follow-up was then conducted on each of these reports. The results were to be sent to the Food and Drug Administration and a copy kept on file within the Drug Information Center.

The result of this policy has been the submission of seven reports between July 1979 and December 1983, three by physicians and four completed by pharmacists. For the two years prior to July of 1979, there were three adverse drug reaction reports submitted, all from pharmacy personnel. This results in an overall report rate of ten suspected adverse drug reactions in a six-and-one-half year period. During this time there were 76,090 admissions to the University Hospital,

which results in an apparent adverse drug reaction incidence of 0.013 per 100 admissions.

Several inpatient adverse drug reaction studies have demonstrated much higher incidences of adverse drug reactions. For example Wang et al[1] utilized an active means of surveillance and review that identified 128 adverse drug reactions among 8291 patients reviewed over a 12 month period, resulting in an incidence of 1.54%. Other surveillance studies using active methods of review including those of Smidt et al,[2] Ogilvie et al,[3] Hurwitz et al,[4] and Seidl et al,[5] revealed adverse drug reaction incidences of 3%, 26.4%, 11.12%, and 25.8%, respectively. Further, a voluntary system of adverse drug reaction reporting conducted by Schimmel[6] revealed an incidence of 9.5%.

Most of these studies used active methods of review and reporting of adverse drug reactions instead of voluntary methods. Such active methods of review and reporting involve the use of a trained professional or paraprofessional to conduct chart reviews and personal interviews with physicians, nurses, and patients in an attempt to identify the occurrence of adverse drug reactions. The advantages of the active reporting methods over voluntary methods are greater recognition, reporting and follow-up of adverse drug reactions. However, increased personnel time, cost and a lack of widespread coverage of patient populations, therapies, and pathology constitute major drawbacks to the use of active methods of monitoring and reporting.

Despite the increased rate of reporting and decreased need for follow-up with active reporting, voluntary methods can potentially monitor greater numbers of patients at a lesser cost. Still, the voluntary systems are dependent on the suspicion or recognition of

potential adverse drug reactions by health care personnel and their awareness of the need for reporting.

A comparison of published incidence data and the incidence of adverse drug reactions reported with University Hospital leads to the logical conclusion that many adverse drug reactions are unrecognized or unreported. This lack of spontaneous reporting and/or recognition is disconcerting, as adverse drug reactions increase morbidity, mortality, hospital admissions,[5] length of stay,[6] and cost per hospitalization.[7] It is also not unreasonable to infer that adverse drug reactions could be implicated in the additional prescribing of medications; with physicians attempting to treat the unrecognized adverse drug reaction with additional drug therapy.

This lack of spontaneous reporting may be attributed to various reasons, including: 1) the reactions may not be recognized as being drug-induced, 2) an adverse drug reaction considered unimportant may not be reported, 3) reporting an adverse drug reaction may be perceived as an admission of poor medical practice or increased liability, 4) personnel may have a poor understanding of the reporting form and/or method, 5) they may be apathetic or indifferent to the need for reporting, 6) the "nuisance factor" of filling out and filing an adverse drug reaction report.

It is this last reason for nonreporting, the nuisance factor, which raises the question of whether a more obvious and readily accessible means of voluntary reporting would provide an increased incidence of reporting. Indeed, to evaluate the influence that complexity of the reporting form has on compliance, the Food and Drug Administration developed a shortened version of their Adverse Drug Reaction Experience

Reporting Form (form #1639a). However, to date there have been no published data verifying or suggesting a difference in reporting incidence relative to the length of the reporting form.

It was for these reasons (i.e., the question of accessibility and visibility of the forms, complexity of forms, and the low incidence of reported adverse drug reactions at University Hospital) that the need was realized to identify a voluntary reporting system which could and would be adhered to by the medical staff. This system needed to serve as a marker to raise suspicion about potential adverse drug reactions. These needs were recognized through the concern and desire for a system that would facilitate the proper monitoring of adverse reactions to drugs. Furthermore, recommendations made to the University of Utah Hospital Pharmacy at a recent inspection by the JCAH stated "the University of Utah Hospital is in need of a method assuring better compliance with the adverse drug reaction reporting system".

Thus, the objectives of this study were 1) to assess the general compliance rate of a more accessible reporting system, 2) to determine whether the format of a short form versus a long form is more acceptable to physicians, 3) to compare the incidence of reported adverse drug reactions using a reporting form to the incidence of adverse drug reactions reported in the medical record, and 4) to compare the incidence of adverse drug reactions with the new system versus the incidence for the prior system.

POPULATION AND METHODS

The study population consisted of all physicians caring for inpatients on 4 North and 5 North nursing units of the medicine service during the defined eight week study period.

This descriptive pilot study examined the reporting of suspected adverse drug reactions. (NOTE: Suspected adverse drug reactions were emphasized in any communications with physicians to eliminate the need for dechallenges, rechallenges, temporal and causal relationships, and the potential for interpretation differences.) Furthermore, the definition of an adverse drug reaction used in this study and communicated to physicians was from Kramer et al.[8] The definition states "an adverse drug reaction is an undesirable clinical manifestation that is consequent to and caused by the administration of a particular drug. The clinical manifestation may be an abnormal sign, symptom, or laboratory test, or it may be a cluster of abnormal signs, symptoms, and tests."

During the defined eight week study period all patients admitted to the 4 North and 5 North nursing units had one of two styles of reporting forms randomly placed in the front of their charts by the unit clerk (Appendices 1 & 2). Each form was labeled "Report For Suspected Adverse Drug Reaction(s)", and included instructions for the unit clerk explaining proper distribution and collection. Further instructions to physicians included the fact that the forms were not intended as permanent additions to the patients' charts, and would be removed upon their discharge. These forms were also distributed to all charts of existing inpatients on the two units. The forms were intended to be distributed by the unit clerks, who received a stack of forms in which the long style and short style forms had been alternately placed. At the beginning of the study each unit clerk received a memorandum and a personal briefing by the investigator explaining the appropriate distribution and collection of the forms. Furthermore, weekly checks

of the inpatient charts were made by the investigator to assess unit clerk compliance, as well as to place forms in those charts lacking them. Also, in order to assure optimal collection of forms from the charts of discharged patients, the medical records specialist serving the two study units was asked to collect any study forms that were not previously removed from the patient charts.

The forms were to be collected upon suspicion of an adverse drug reaction, or upon termination of the patients' inpatient stay. If there were no suspected adverse drug reactions, the physician was to check the box labeled "no suspected adverse drug reaction". However, if there was a suspected reaction, the form was to be filled out completely.

The housestaff physicians were notified in writing of the implementation of the reporting system, their proposed role in completing the forms, and that various form styles would be tried initially. Memoranda were distributed to all housestaff physicians prior to, and at the midpoint of the study period (Appendices 3 & 4). The memorandum distributed at the midpoint of the study also included an update of any reported adverse drug reactions during the first half of the study.

The final step in this study involved a chart review conducted by the investigator. Fifty charts were randomly selected from those of patients discharged from the study units during the study period. This review focused on all progress notes and discharge summaries written regarding the specific hospital admission for which a reporting form had been distributed and collected. This review was conducted with the intention of detecting any mention of a suspected adverse drug reaction, which may have taken place during the patient's hospitalization. Also,

any suspected adverse drug reaction that may have lead to the current hospitalization was noted.

The data analysis for this study consisted of descriptive information involving the number of forms distributed and collected, and the number of adverse drug reactions reported in charts and on forms (Table 1). The calculations performed on the data included:

$$\text{Physician Compliance Rate} = \frac{\text{Total \# of forms completed (+ or -) for ADR} \times 100}{\text{Total \# of forms distributed and collected}}$$

$$\text{Form versus Chart Reporting} = \frac{\text{\% of suspected ADR reported on forms}}{\text{\% of suspected ADR reported in charts}}$$

$$\text{Comparison of Reporting Systems} = \frac{\text{Incidence of reported ADR in current study}}{\text{Prior incidence of ADR for University Hospital}}$$

RESULTS

During the eight week study period, equal numbers of short and long style forms were distributed to the study units. During the study, 259 forms were distributed to patient charts and collected upon their discharge. Eighty-eight of these forms were recovered by the medical records specialist. Within this same period there were 488 discharges, giving a compliance rate for unit clerks distributing and collecting forms of 35% (259 - 88 forms/488 potential).

The number of suspected adverse drug reactions reported during this study was two. Neither of these positive reports for adverse drug reactions were appropriately completed, with the majority of elements on each form remaining unanswered. There was one form checked as

having "no suspected adverse drug reaction", therefore 256 forms remained blank. This number of adverse drug reactions reported in conjunction with the total number of forms distributed to charts and collected, was used to determine the reported incidence of suspected reactions. This incidence of reported suspected adverse drug reactions was 0.77%. In comparison, the prestudy incidence was 0.013%. Of the 50 charts reviewed for the presence of suspected adverse drug reactions, 22 had one or more suspected reactions reported. Thus, the incidence of suspected adverse drug reactions in the charts for this representative sample was 44%. Furthermore, the one form which indicated "no suspected adverse drug reaction" was from a chart in which a suspected adverse drug reaction was noted.

The study objective of comparing reporting incidence with the short form style versus the long form style was unattainable, as only one suspected adverse drug reaction was reported on each form type. The physician compliance rate for the number of forms completed (+ or -) for adverse drug reactions was 1.2%. The degree of reporting on forms versus charts was 0.0175.

DISCUSSION

There were several inherent problems with this study. The eight week study period was much shorter than most of the published studies.[1-6] Because of this shorter period, the sample was too small to allow statistical analysis. The unit clerk compliance for distributing and collecting the reporting forms was very poor. This occurred despite the prior authorization of the Pharmacy and Therapeutics Committee, Nursing Administration, Medical Records Director, and Floor Charge

Nurses for the units utilized in the study. There were several reminders given to unit clerks by the investigator.

The incidence of suspected adverse drug reactions reported in this study was much greater than the incidence prior to the study, (0.77% versus 0.013%). It is important to note that the 0.77% was calculated by dividing the number of suspected adverse drug reaction reports by the number of report forms distributed to patient charts and collected, whereas, 0.013% was arrived at by dividing the number of reports by total patient admissions. This was done because it was felt the new reporting system was designed for high visibility and accessibility, and therefore could only be assessed in relation to actual exposure to the reporting forms. Despite the higher reporting incidence, the number of responses to the forms (+ or -) for the presence of suspected adverse drug reactions was very low, with only three responses out of 259 possible. This still raises the questions of whether the physicians felt the adverse drug reactions were unimportant, whether they increased professional liability, or whether apathy or the "nuisance factor" was the cause of the low incidence of reporting. However, in reviewing the patient charts it became evident there are a great many suspected adverse drug reactions that are noted yet never reported on the forms. This suggests physicians do find adverse drug reactions important and are not concerned with the liability issue. It may be that the physicians felt unfamiliar with the reporting form and new system. This appears to be unlikely in view of the two memoranda explaining the forms and systems, and the constant high visibility and accessibility of the forms.

An interesting addition to the present study would have been the inclusion of a questionnaire to the housestaff asking for a preferred method of adverse drug reaction reporting, as well as their views on the recently studied system. Other points of interest which could not have been determined in this study due to time constraints are whether the reporting incidence increases or decreases with familiarization with the process, if the presence of a more visible adverse drug reaction reporting system would heighten awareness and suspicion, and whether periodic bulletins and inservices to the medical staff on the monitoring of drug therapy would result in increased reporting.

CONCLUSIONS AND RECOMMENDATIONS

The physician compliance rate for this highly visible and accessible system was very poor. The objective of determining the acceptability of a reporting form with a long format versus a short format was unattainable. The study also reveals that physicians report suspected adverse drug reactions much more readily in patient charts than on reporting forms. Also, the apparent incidence of adverse drug reactions reported with the new system was much higher than the prior system.

The low compliance rate for this system suggests a lack of cooperation or a misunderstanding of the new reporting system. The unattainable objective analyzing form length failed because of the low incidence of reporting and the short period over which the pilot study took place. This study suggests that the reasons for the low incidence of adverse drug reaction reporting on forms are the nuisance involved, indifference, or the misunderstanding for the need of reporting in both the chart and form.

Because of these proposed reasons for nonreporting, and the increased reporting incidence of the new system over the previous, it should be quite useful to conduct another pilot study which utilizes physicians in designing a more acceptable form. This involvement should help reduce problems of misunderstanding and indifference. Further, the pilot study should include a questionnaire directed to physicians' feelings regarding the reporting form and system. In light of the higher incidence of spontaneous adverse drug reaction reporting in the medical record, perhaps an active surveillance program involving chart review will give rise to a more acceptable adverse drug reaction surveillance program.

TABLE 1

STUDY DATA

	4 North	5 North	Total
Number of forms distributed to floors	170	230	400
Long style	85	115	200
Short style	85	115	200
Number of forms distributed to charts and collected	-[a]	-	259
Number of forms remaining in charts at termination of study	1	8	9
Number of unused forms returned to investigator	33	27	60
Number of forms unaccounted for	-	-	63
Number of patient admissions during study period	212	221	433
Number of patient discharges during study period	258	270	528
Number of suspected ADR's[b]	-	-	2
Number of forms with responses (+ or -) for ADR's	-	-	3
Number of charts reviewed	-	-	50
Number of charts having one or more suspected ADR's	-	-	22

a - specific unit data unavailable b - ADR (Adverse Drug Reaction)

TABLE 1

STUDY DATA

	4 North	5 North	Total
Number of forms distributed to floors	170	230	400
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Number of forms remaining in charts at termination of study	1	8	9
Number of unused forms returned to investigator	33	27	60
Number of forms unaccounted for	-	-	63
Number of patient admissions during study period	212	221	433
Number of patient discharges during study period	258	230	488
Number of suspected ADR's[b]	-	-	2
Number of forms with responses (+ or -) for ADR's	-	-	3
Number of charts reviewed	-	-	50
Number of charts having one or more suspected ADR's	-	-	22

a - specific unit data unavailable

b - ADR (Adverse Drug Reaction)

APPENDIX 1

ATTENTION: Unit Clerk, please place form in patient's chart at time of admission (with patient Hospital # on it) and remove form at time of discharge.

Report for Suspected Adverse Drug Reaction(s)

1) Patient Hospital I.D. number?

2) Did this patient experience a suspected ADR?

No Suspected ADR ___ No further questions need be answered.

If yes -- please complete form accordingly.

3) What was the date of reaction onset?

4) What was the suspected reaction?

5) What is/are the responsible drug(s)?

6) Did this reaction alter therapy? If so, how?

7) Comments (including other suspected ADRs).

This form is not part of patient's permanent medical record and will be removed from chart at time of discharge.

APPENDIX 2

ATTENTION: Unit Clerk, please place form in patient's chart at time of admission (with patient Hospital # on it) and remove form at time of discharge.

Report for Suspected Adverse Drug Reaction(s)

1) Patient Hospital I.D. Number:

2) Did this patient experience a suspected ADR?

No suspected ADR ___ No further questions need be answered.

If yes -- Please complete form accordingly.

3) What was the date of reaction onset?

4) What was the suspected reaction?

5) What is/are the responsible drug(s)?

6) What was the reason for use of the drug?

7) Route?

8) Daily dose?

9) Date of first administration?

10) Were other drugs taken concomitantly? If so, which?

11) Comments (including other suspected ADRs)

12) Did this reaction alter therapy? If so, how?

13) Physician's name:

This form is not part of patient's permanent medical record and will be removed from chart at time of discharge.

APPENDIX 3

M E M O R A N D U M

TO: Housestaff Physicians

FROM: Pharmacy and Therapeutics Committee

DATE: March 5, 1984

SUBJECT: Adverse Drug Reaction (ADR) Reports

Within the next week all charts for inpatients shall contain an additional form. This form will be part of an Adverse Drug Reaction Reporting System for the University of Utah Hospital. It would be most helpful if any physician caring for an inpatient would fill out the questionnaire at the time of patient's discharge, or earlier if there is suspicion that an ADR is occurring or has occurred. If it was felt that the patient did not experience an ADR, then please check the box indicating "No Suspected ADR" and no further questions need be answered. However, if it is felt that the patient may have experienced a suspected ADR**, then please complete the form accordingly.

These forms are being implemented as fulfillment of JCAH requirements (which were reiterated to the Pharmacy and Therapeutics Committee at the recent site visit). In order that we may all benefit more directly from these forms, a memo will be distributed to you every two weeks to report on the responses to the system (i.e., number and type of ADRs reported). Initially, forms will only be distributed to 5N and 4N medical floors.

These forms are NOT intended to be part of the patient's permanent medical record and will be removed from the chart at the time of patient's discharge. They will then be examined by the Pharmacy and Therapeutics Committee. Various forms will be tried initially, therefore, please fill out a form for every patient upon his/her discharge.

Your compliance with this system will be greatly appreciated and will benefit us all.

For further information please contact the Drug Information Center, Ext. 2073.

**Adverse Drug Reaction (ADR) -- An ADR is an undesirable clinical manifestation that is consequent to and caused by the administration of a particular drug. The clinical manifestation may be an abnormal sign, symptom, or laboratory test, or it may be a cluster of abnormal signs, symptoms, and tests.

These reports need not be for verified ADRs, but rather the suspicion that one may have occurred.

APPENDIX 4

M E M O R A N D U M

TO: Housestaff Physicians

FROM: Pharmacy and Therapeutics

DATE: April 23, 1984

SUBJECT: Adverse Drug Reaction (ADR) Reports

During the past 5 weeks Adverse Drug Reaction Reporting forms have been distributed to all inpatients on 4 North and 5 North. These forms are part of an Adverse Drug Reaction Reporting System for the University of Utah Hospital. They were implemented as fulfillment of JCAH requirements and the need for greater awareness of ADR's.

It is most helpful if any physicians caring for an inpatient would fill out the questionnaire at the time of patient's discharge, or earlier if there is suspicion that an ADR is occurring or has occurred. If it was felt that the patient did not experience an ADR, then please place a check-mark in the spot indicating "No Suspected ADR" and no further questions need be answered. However, for suspected ADR's please complete the form accordingly.

To date only 1 ADR has been reported; this involved the local infiltration of Conray 43 (IV contrast dye) into soft tissue. The subsequent reaction resulted in local sloughing of skin.

These forms are NOT intended to be part of the patient's permanent record and will be removed from the chart at the time of patient's discharge. They will then be examined by the Pharmacy and Therapeutics Committee.

For further information, please contact the Drug Information Center, extension 2073.

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7) Venulet J. Methods of monitoring adverse reactions to drugs. Prog Drug Res 1977;21:231-292.

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CURRICULUM VITAE

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PERSONAL

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EDUCATION AND TRAINING

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