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ANALYSIS OF THE CLINICAL RESEARCH METHODOLOGIES EMPLOYED DURING A PHASE THREE EFFICACY STUDY FOR ULTRACET AS A POST-HERNIORRHAPHY ANALGESIC

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THESIS

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CHAPTER I

INTRODUCTION

Early surgical intervention consisted of the patient having to endure elevated levels of pain and stress. Consequently, early civilizations appreciated the importance of pain management by employing their current knowledge and resources available to them in their corresponding environments. In ancient Greece, "Hypnos was the most welcome of gods in sorrow and sickness, and especially during the pain of operative surgery (Robinson, 1946)." This method of pain relief, which was based on belief systems, quickly evolved to include more empirical applications.

Greek physicians, in order to produce loss of consciousness in their patients, would compress the principal arteries of the neck. The Greek word carotid signifies drowsiness thus, in medical terminology one of the main arteries in the neck is labeled as the carotid artery. Later, Greek physicians would discover the analgesic and somnolescent properties of wine, hemp, and poppy. However, such substances were not employed during surgery due to the unpredictable outcomes experienced by many patients. Celsus, a prominent Roman physician wrote, "Pills are so numerous, and are made for various purposes. Those which relieve pain through sleep are called anodynes; unless there is overwhelming necessity, it is improper to use them (*De Medicina*, first centuryA.D.)." Robinson (1946) indicates that these substances were used more by poets and dramatists than by physicians. It is evident that the uses of analgesic substances were

limited in the treatment of surgical repairs during the early years of medical science, however surgical procedures continued to evolve regardless of anesthesia and analgesics.

Hernial defects have distressed humans since the origin of our species. The management of hernial discomfort can be traced back to the ancient Egyptians 3,500 years ago, as they would mitigate their pains with tight fitting bandages and trusses (Lichtenstein, 1986). Celsus, the great Roman surgeon, was the first to make a small incision in the scrotum or groin, separate the hernial sac from the spermatic cord, and orchiectomize the hernia patient (Lichtenstein, 1986). The surgical advances that were taking place in the treatment of hernia defects, as well as other operable conditions of that time, began to decrease as religious prejudice against mutilation of the body emerged after the fall of the Roman Empire.

The Popes that influenced the post-Roman era prohibited the art of surgical intervention until medieval times when the Borgia and Medici Popes allowed the dissection of human cadavers for anatomical correctness of paintings and sculptures (Lichtenstein, 1986). During medieval times, Theodoric of Cervia used a *spongia somnifera* during hernia surgeries. The *spongia somnifera* was a sponge that was saturated with opium, mulberry, hyoscyamus, mandragora, and lettuce seeds (Robinson, 1946). However, the efficacy of the sleeping sponge is questionable since Theodoric's patients would be completely strapped to the operating surface from the chest down. Unfortunately, during the middle ages, improvements in surgical and post surgical pain management did not flourish, for it was the religious notion that pain was necessary for the salvation of one's soul.

Once Lister's carbolic acid spray antisepsis was implemented in surgical theatres, hernia repairs were no longer performed superficially through the external ring of the inguinal area. Edoardo Bassini from Pavia, Italy performed the first true herniorrhaphy in 1884. Due to the fact that his surgical technique yielded low mortality and recurrence rates, bright surgeons such as Sir Astley Cooper and William Stewart Halstead modified Bassini's successful approach in order to comply with the different variations and demands of hernia defect anatomy.

William Stewart Halstead from Johns Hopkins University utilized cocaine as a local anesthetic during hernia repairs as well as for post surgical pain. His progress and innovations in the development and application of surgical analgesics came to an abrupt stop after he became addicted to cocaine (Robinson, 1946).

In most recent times there has been a systematic approach in developing and improving the different modalities and constituents of healthcare. Such systematic approaches emphasize the safety and improvement of a patient's condition. There is early indication of attempts to measure patient outcomes and concerns. During the mid 1800's, Florence Nightingale kept logs of patient reactions and opinions to modifications in medical treatment as well as formulating statistics for these responses (C.L. Ireson and R.W. Schwartz, 2001). Shortly after, Boston surgeon E.A. Codman layed foundation for one of the first peer-review systems through quality assurance of healthcare (Robinson, 1946).

In a recent study conducted by D. Casarett et al., there is mention of the different elements that established strict guidelines for clinical pain research. In the United States,

the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) required investigators to explicitly state the intentions and structure of the study as well as its possible advantages and risks. The Declaration of Helsinki was the first document of its kind to set global rules of conduct for the treatment of human subjects involved in a scientific research (World Medical Association, 2000) which, along with the Nuremberg code of 1947, will prevent atrocities and exploitation of vulnerable individuals.

According to a study carried out by Puig et al. (2001), the management of postoperative pain is sub optimal worldwide. The study consisted of sending surveys to hospitals in Europe and the United States. The questionnaire included inquiries regarding surgical workload, surgical specialties, resources for pain treatment, pain assessment and drug treatment. An observation noted in the study was that there was non-compliance in responding to the questionnaire on behalf of several private hospitals surveyed in the United States. This may reflect reluctance to participate in external audits (Puig et al., 2001). The results of the study indicate that postoperative pain assessment only occurs in thirty six percent of patients in Spain. Other studies performed in Italy and the United States indicate that postoperative pain assessments are performed on fifty-five percent of patients and thirty-nine percent of patients correspondingly (Puig et al., 2001). There is evidence that postoperative pain assessment improves postoperative treatment (Puig et al., 2001). In response to inappropriate postoperative pain management in the United States, studies such as *A comparison of the Analgesic Efficacy of Ultracet (Tramadol HCL/Acetaminophen) Versus Tylenol with Codeine Number Three Versus Placebo for the*

Treatment of Post surgical Pain are being conducted. This study utilizes ventral and inguinal hernia repairs as a model for a prospective postsurgical analgesic. This is due to the fact that these types of procedures require the use of oral analgesics in current practice. Other procedures, such as open-heart surgery, would require more potent intramuscular analgesics as opposed to oral pain medications. The goals are to provide an efficacious and cost accessible postoperative analgesic with low incidents of side effects. There have been similar studies that have attempted to fulfill the mentioned objectives, but have obtained no significant results.

For example, in a study performed by Gill et al. (2001), pre-emptive analgesia via administration of a field block of bupivacaine for postoperative herniorrhaphy pain was attempted. The premise behind this experiment was based on the fact that postoperative pain is caused by an increase in dorsal horn neuron stimulation from tissue insult (Gill et al., 2001). By administering a bupivacaine block either after induction but before surgery or after surgery but before the end of anesthesia, dorsal horn excitability may be reduced. As a consequence, one would obtain a cost-effective and efficacious postoperative analgesic (Gill et al., 2001). The results of this study demonstrated that pre-emptive analgesia can not be obtained by bupivacaine field block injections. This may be attributed to the short half-life of the local anesthetic (Gill et al., 2001). The current Ultracet pain study does not focus on obtaining pre-emptive analgesia; rather it is compared to other active agents that have shown efficacy independently.

CHAPTER II

JOURNAL OF THE INTERNSHIP PRACTICUM

In the introductory meeting, Della Weis RN BSN introduced me to the surgical staff of the Osteopathic Medical Center of Texas (OMC), which included; Don Peska D.O., Adam Smith D.O. and Mark White D.O. A review of the good clinical practices and protocols of the pending and current medical trials was performed. At approximately 3:00 P.M, there was a brief meeting with Ms. Judy Brown, the Pharmaceutical Resource Corporation site manager hired on behalf of Ortho-McNeil Pharmaceutical Company. The meeting consisted of review of the completed patients involved in the post-operative pain medication following inguinal hernia and ventral incisional hernia repair. At 4:45 P.M, Ms. Della Weis R.N BSN and myself attended to the post –operative follow up of Ms. J., a post-operative pain medication study participant. The remaining test drug was collected by Ms. Della Weis R.N BSN and counted by the clinical research coordinating team. Adam Smith D.O., the principal investigator of the postoperative pain medication study, finalized Ms. J's participation questionnaire.

May 14, 2001

I reported to the OMC of Texas' operating room supervisor, Dale Gibson R.N. for Mr. M's right inguinal hernia repair with mesh and plug. Immediately after the surgical repair, Mr. M. was asked about his pain perception on a visual analog scale from one to ten. He reported mild pain at approximately a level four on the scale. Upon arrival to the

patient's room, he reported moderate pain at level four of the described scale. At that time, he was given the randomized double blind study drug at 9:50 A.M. At 10:20 A.M. and 10:50 A.M. I asked Mr. M. to answer the questions on the questionnaire that read as follows:

"Please rate the post surgical pain intensity that you are currently experiencing."

"Please rate your current pain relative to your pain before you took the first dose of study medication." He reported the same pain perception on the pain visual analog scale.

May 17, 2001

I reported to the operating room at the OMC of Texas at 7:00 A.M. to meet German Berbel D.O. for the left inguinal herniorrhaphy of Mr. M. Due to the fact that Mr. M. did not feel any pain relief after administration of the study medication, he was discontinued from the study at 11:25 A.M. This was primarily due to an increase in blood pressure, nausea, and vomiting. For his pain and emesis, he was given an intramuscular injection of Phenergen (12.5 mg) and Demerol (25 mg). It was pleasant to see that Mr. M's discomfort was greatly mitigated by the intramuscular injection.

May 18, 2001

After reporting to the Patient Care Clinic office of Dr. Adam Smith, I was responsible for obtaining Mr. T's temperature, pulse, and blood pressure after I had explained the informed consent document for the experimental drug trial that he agreed to participate in. Secondly, a complete family history of ailments was recorded followed by

his personal medical history. He expressed concern about the possibilities of obtaining a placebo. Mr. T. received notice that the study is a double blind study and that such knowledge is not shared with the clinical research coordinator or any member of the surgical team. The reason for the blind is to maintain scientific integrity through elimination of sample bias.

May 21, 2001

I reported to the operating room of the OMC of Texas at 6:30 A.M., where Mr. T. underwent a repair of his right inguinal hernia. After 2 hours of administration of phentanyl, a drug used for surgical pain, he was randomized when he reached a moderate rating of four on the visual analog scale. After taking the study medication, Mr. T. expressed that his pain was less than before he took the medication. After monitoring him for four hours, he expressed a satisfactory decrease in his post surgical pain when compared to the initial dose of the study medication. He was sent home with a study medication questionnaire and journal at 1:30 P.M.

May 22, 2001

Mr. R. reported to the OMC of Texas at 6:15 A.M. for his left inguinal hernia repair. Mr. R. was placed under general anesthesia for Dr. Berbel's herniorrhaphy. Following the surgical intervention, Mr. R. was taken to the recovery room where he began to express pain. After the surgical analgesics had completed their half-life, the study medication was given to Mr. R. Shortly after, Mr. R. became nauseated and

reported a nine on the pain visual analog scale. Due to the symptomology and evident distress, he was discontinued from the pain medication study a 10:26 A.M.

May 23, 2001

At 10:30 Ms. H. reported to the University of North Texas Health Science Center's Patient Care Clinic where the informed consent document was read, signed, and initialed as the patient progressed through each page. Her questions regarding the informed consent were answered. Inclusion and exclusion criterion were reviewed. Vital signs were measured, followed by the gathering of her family history and concomitant medications. The patient was advised to contact the Patient Care Clinic for any questions or concerns.

May 24, 2001

At 8:30 A.M., I reported to the OMC of Texas' operating room where Ms. H. underwent her right inguinal hernia repair. Unfortunately after the surgery and administration of the study medication, she did not obtain sufficient analgesia. As a consequence, 25mg/ml of Demerol was given at 12:25 P.M. Termination of Ms. H. as a pain study subject was inevitable and her discharge was identified as being a result of lack of drug efficacy.

May 30, 2001

Mr. T. was introduced to the clinic at 1:45 P.M. His weight, blood pressure, and pulse were measured. Secondly, the study medication was retrieved from Mr. T. following his collection of the final assessment of the study journal. Promptly afterwards, Dr. Berbel inspected the patient's incision as well as his overall recuperation. The patient had questions regarding his surgical procedure, and Dr. Berbel answered them to the patient's satisfaction. Mr. T. was advised to return in one week for further analysis.

Today, Mr.V. arrived to the OMC of Texas in order to complete his pre operative appointment. At that time, the informed consent was read, explained, and signed by him. There was concern about his eligibility in the pain study due to the fact that he had been taking benzodiazepines for his generalized anxiety. There was a concern that such medication would confound the efficacy of the pain medication when administered. Ortho-McNeil Pharmaceuticals was called for approval of the patient as a pain study subject. Ortho-McNeil Pharmaceuticals approved Mr. V's participation.

June 4, 2001

The objectives for today were to review protocols for their possible implementation into a clinical research trial at the University of North Texas Health Science Center's department of surgery.

June 11, 2001

Ms. H's preoperative visit began with her reading the informed consent document. She was encouraged to ask for clarification at any point during her review of the informed consent document. Secondly, her medical and family histories were obtained once she signed the informed consent followed by instructions on how to keep the postoperative assessment journals. She was concerned about how her appearance would result after her ventral incisional hernia repair. She was advised to voice her concern to Dr. Berbel before her surgical procedure.

June 12, 2001

Dr. Berbel scheduled Ms. H's ventral incisional hernia repair at 7:30 A.M. During the procedure, there was personal notice that such repairs require a larger incision. Shortly after the surgery, Ms. H. experienced unbearable pain that resulted in an intramuscular injection of fentanyl. As time elapsed, she continued to have constant and severe pain as well as more intramuscular fentanyl injections. Unfortunately, her pain was not mitigated with fentanyl nor morphine injections. Overall she was given 250 ug of fentanyl and 15 mg of morphine before there was a decision of discontinuing her from the pain study. Due to her lack of analgesia from morphine and fentanyl, Ms. H. was discontinued from the pain study.

June 13, 2001

Mr. T's preoperative session of his right inguinal hernia repair began by explaining the informed consent document and emphasizing the importance of seeking clarification of any concept mentioned in the informed consent document. Once the informed consent was signed, I obtained his medical and family history. He mentioned that he had an increased pain threshold due to his long career as a professional soccer player and member of the Yugoslavian national soccer squad. He displayed eagerness in participating in this pain study. Finally, explanation of the post-operative assessment journals took place.

June 14, 2001

Dr. Snow began Mr. T's right inguinal hernia repair at 8:30 A.M. His hernia was relatively small when compared to other study patient hernias. After the half-lives of the surgical analgesics expired, he was asked to rate his pain on the pain visual analog scale. He quickly reported a moderate two rating on the visual analog scale. He was advised to report his pain condition in a frequent manner. He began to feel a pain reading of four on the pain visual analog scale at 11:30 A.M. Mr. T. was given the study medication and monitored according to the clinical study protocol. Mr. T. reported a significant decrease in pain at the end of the patient monitoring session.

CHAPTER III

DISCUSSION

The Ortho-McNeil Company is studying the post surgical analgesic efficacy of the drug Ultracet (tramadol HCl/acetaminophen). The University of North Texas Health Science Center at Fort Worth department of surgery is one of the sites where this multicenter, randomized, double blind, active controlled and placebo controlled, parallel study of subjects with post surgical pain is being conducted. The study drug's (37.5 mg tramadol HCl/325 mg acetominophen) efficacy will be determined by comparing it with the analgesic efficacy of Tylenol with Codeine number three (30 mg codeine phosphate/300mg acetaminophen) and a matching placebo.

The goal of pain studies is to transfer knowledge from efficacy studies using randomized controlled trials into the clinical setting (C.L. Ireson and R.W. Schwartz, 2001). The means by which this is accomplished is by measuring outcomes in terms of their medical treatment and by fulfilling the requirements established by the Food and Drug Administration. More specifically and in this case, measuring the outcomes of surgical patients is of prime importance because these interventions are designed to relieve symptomologies and discomforts associated with a specific disorder (C.L. Ireson and R.W. Schwartz, 2001).

Due to the time and economical demands set by managed care principles on healthcare delivery, new pharmaceuticals and services must be modified to meet these demands in an ethical and efficacious manner (C.L. Ireson and R.W. Schwartz, 2001).

Jenkins et al. (2001) postulated that "obtaining patient perceptions may be more economical and reliable than traditional methods of assessing quality." In the study performed by Jenkins et al. (2001), a questionnaire was formulated and given to 355 patients preoperatively and asked to rank ten postoperative outcomes that they would prefer to avoid. The following postoperative outcomes were ranked on a scale from one to ten, with ten being the most upsetting and one being the least upsetting: a normal outcome, thirst, gagging on the tracheal tube, drowsiness, sore throat, shivering, disorientation, pain, nausea, and vomiting. The results indicated that pain was the most upsetting postoperative outcome.

The study, *A comparison of the Analgesic Efficacy of Ultracet (Tramadol HCL/Acetaminophen) Versus Tylenol with Codeine Number Three Versus Placebo for the Treatment of Post surgical Pain* addresses such result. This is a phase three study, which is characterized by performing the postoperative analgesic study within a specific patient population along with the anticipated dose that will be commonly used in the clinical setting.

As described in the journal of the internship practicum, certain procedures performed demonstrate the meticulous application of the rules dictated by regulatory entities as well as good clinical practices. At the initiation of the internship (May 8, 2001), review of good clinical practices was imperative for the purposes of awareness as one interacts with the study patients. Emphasis is made on patient understanding of the pain study protocol and patient confidentiality.

In order to enroll patients in a clinical pain study, inclusion and exclusion criteria must be met. These criteria are protocol specific, meaning that the company sponsoring the study specifies requisites and parameters in the study protocol. For example, on May 23, 2001, Ms.H's inclusion and exclusion criteria were reviewed to verify that she would meet the protocol requirement of having a negative urine pregnancy test up to five days prior to study entry. Another matter that pertains to inclusion and exclusion criteria can be demonstrated when on May 30, 2001, Mr. V's benzodiazepine medication was analyzed for inclusion criteria fulfillment. The concern was having the benzodiazepine medication, which was prescribed for generalized anxiety, confound the post surgical analgesic survey of the pain study. The protocol for this study clearly indicates that subjects who require the concomitant use of sedatives or analgesics other than those used during surgery or subjects with a significant psychiatric disorders should be excluded from the study. In order to verify his inclusion or exclusion status, the Ortho-McNeil Pharmaceutical Company was briefed on Mr. V's medication and asked for participation status.

The most crucial element in any clinical research endeavor is the informed consent document. No procedures or tests can be performed without the informed consent from a potential pain study subject. This document gives the potential study subject an opportunity to review important details of the study and inquire about the fine points indicated in the informed consent document. On May 18, 2001, Mr. T's informed consent was obtained after having him read and initial every page of the informed consent document and after answering his concerns. During this preoperative visit, the

required elements of an informed consent document were addressed. The document must include the following: the purpose of the study, duration, number of visits required, benefits and risks of study treatment, side effects of pain study medication, probabilities of receiving a placebo, alternative treatments that may be beneficial for the patient, indication that the subject has the right to withdraw with no penalty, contact information, confidentiality measures, compensation opportunity, and explanation of the different medical interventions that are available in case of an injury suffered during the pain study (Norris, 1994).

When discussing the informed consent document, the clinical research assistant and coordinator need to address the information that is most important to the patient, assuming that all the elements of the informed consent document have been reviewed by them. Two basic challenges in the informed consent process are to find out how much and what kind of information the research patient wants to know (Casarett et al., 2001). In a study carried out by Casarett et al. (2001), these challenges were approached by asking forty patients to contemplate about " ways in which being in the study might be helpful or harmful and what information they would want before deciding whether to enroll in a clinical pain study." These questions were phrased in an open-ended manner in order to minimize bias (Casarett et al., 2001). The results of this informed consent study indicated that the greatest concerns involved how to take the pain study medication, the requirements for supplemental study appointments, and the general side effects of the pain study medication (Casarett et al., 2001). The information from this study is valuable for the recruitment of viable pain study patients. Having a study population that is

compliant and has a decreased rate of discontinuation will allow an increase in generalizability of the pain study results (Casarett et al., 2001).

In this particular Ultracet pain study, a pain visual analog scale was used to measure the pain perception of patients postoperatively. For example, on May 21, 2001 Mr. T's pain was surveyed in order to fulfill the inclusion criteria stating that the subject must have at least moderate post surgical pain and a reading of four (40mm on the pain visual analog scale) in order to receive the pain study medication. Since surgical patients' postoperative course improves as time elapses, a pain visual analog scale was considered appropriate for obtaining quantitative data from qualitative pain perception responses (C.L. Ireson and R.W. Schwartz, 2001). Along with this analog scale, a Wong-Baker FACES pain rating scale is provided for patient pain rating. The FACES pain rating scale is considered accurate in its facial representations of pain among adults (Graven-Nielsen et al., 2000).

One of the reasons for monitoring the study patient for four hours after surgery is to assess the progress of the patient's postoperative pain. This assessment will dictate the study drug's efficacy. Another reason is for precautionary measures in case the patient experienced an adverse event or a serious adverse event. An adverse event is defined as any deviation in health when compared to the patient's baseline condition. This change in condition may or may not be attributed to the investigational drug. For example, during the May 22, 2001 post herniorrhaphy repair analysis of Mr. R., he reported being nauseas after he was given the study medication. Previously to his pain medication randomization, he was not nauseated. As a consequence, his post medication nausea was

reported as an adverse event on the case report form as indicated in the pain study protocol.

During the postoperative follow-up, all materials are collected and verified as was done on May 8, 2001. The final health assessment by the principal investigator and the final medication count by the clinical research team are instructed in the pain study protocol. The details of data gathering, study drug administration, inclusion and exclusion criteria, and study closing are termed as being protocol specific.

CHAPTER IV

SUMMARY

The history of pain management stems back many thousands of years. However, not until recent times have significant advancements in biochemistry and pharmacology allowed analgesics to be incorporated in clinical interventions and everyday life. Due to these advancements, attempts to refine pharmacological action on receptors in terms of specificity would render medications with fewer side effects. The technology is present, but the application and development of modern analgesics in post-surgical settings is substandard.

According to C.L. Ireson and R.W. Schwartz, (2001), the outcomes of ailment interventions in the United States are "...no better and in numerous situations worse that those achieved in other countries," even though the United States has the most expensive healthcare in the world. Furthermore, a study performed by Carr et al. (1998), has identified the United States as demonstrating consistent inadequacies in postoperative pain management.

Several factors have been identified as being contributors of poor post-surgical pain control in America. Lack of awareness of the available strategies in acute pain control and its implementation in post surgical care are labeled as being problematic observations (Puig et al., 2001). In response to these conditions as well as the managed health care time and cost limitations, new and efficacious pharmaceuticals must be made available to a broad spectrum of socio-economic strata.

Currently, there is great debate about the use of laparoscopic herniorrhaphy versus open tension free approaches. In terms of cost, the laparoscopic procedure is more expensive and yields less postoperative pain, however the open tension free approaches are less expensive and yield more postoperative pain (Sarli et al., 2001, Medical Research Council Laparoscopic Groin Hernia Trial Group, 2001, Parviz et al.,1995). There are advantages and disadvantages to both procedures. Assuming that efficacious postoperative analgesics were available, the open tension free repair would be more feasible in terms of cost and hernia recurrence rates (Sarli et al., 2001).

In terms of pharmaceutical development, the laws and guidelines by the regulatory agencies such as the Food and Drug Administration, institutional review boards, and pharmaceutical sponsor protocols must be followed. Along with good clinical practice standards, interdisciplinary collaboration in pain studies produce results that are statistically and clinically salient. The patient's well-being and comfort is the ultimate goal in clinical pain studies and in medicine in general, therefore postoperative pain should be aggressively managed.

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