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特別講演

Advances in the Clinical Evaluation
of Analgesics

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INTRODUCTION

Patients with pain of pathological or surgical origin are the subjects of choice for definitive evaluation of analgesics in man. The measurements of pain are subjective and are obtained by patient interview. Patients are asked how much pain they have and an arbitrary rating scale is used to record this information. Visual analog scales, in which the patient indicates the degree of pain, have been used by some, but they have not been proven to be better than direct subjective responses. Experimental pain in man, until very recently, has been completely unrewarding. Newer, experimental techniques have given some promise in evaluating analgesic effect. We do not use experimental pain in our facilities, as we have not found it efficient.

Measurements of subjective responses, such as pain and pain relief in the clinical situation, are subjected to multiple biases. There are differences that exist among patients, both physically in terms of their disease and pain, and psychologically in terms of their expectations. The etiology of the pain appears to have little

bearing on the response. However, some have recently reported that centrally acting narcotics are not as effective in relieving pain from uterine cramps or dental pain, as are the anti-inflammatory drugs. The initial degree of pain influences the response to a test drug. Psychological factors such as what the patient anticipates, can also influence the response. A pathological state with decreasing pain over time, such as in post partum pain or post operative pain, can be another factor. Carry-over effect based on previous therapy can influence the results. Pharmacological variables, such as absorption, dissolution rate, presence of food in the stomach can all have an influence on the patient's response. The ambulatory and non-ambulatory state can be extremely important, particularly in terms of adverse effects. Tolerance and physical dependence to preceding drugs can influence the patient's response to the test drug. The nurse observer may influence the response that is obtained. Randomization may correct many of these variables, but **can not** be fully relied upon, and therefore, all of these factors should be taken into consideration in designing a study.

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METHODOLOGY

We are currently utilizing the following methodology with some slight variation in our facilities in Venezuela, Puerto Rico, Mexico and the United States. Patients are selected who have moderate or severe pain related to child birth, surgery, fractures or musculo-skeletal disease.

They are informed of the study and give written consent to participate. Only patients who are able to communicate with the nurse observer, are selected. Concurrent drugs which could influence the response of the patient are avoided. Certain patients are also excluded because of their history of adverse effects to the drug type under study or because of the disease entity. Women who are breast feeding may not be permitted to enter certain studies, if the concentration in breast milk and the safety of the medication in newborns has not been established. Oral medication is given with a minimum of 240 cc's of water and the patient is asked to sit up or turn on the right side to promote gastric emptying. All medications are given double blind in individual containers so that the patient and the nurse are not aware of the treatment. The patients are interviewed by the research nurse observer and questioned as to the amount of their pain. Two subjective measures of pain are used : intensity and relief. The intensity scale contains 4 points : 0=no pain ; 1=slight pain ; 2=moderate pain ; and 3=severe pain. Patients are interviewed at 30 and 60 minutes after receiving medication, and hourly thereafter for a total period of observation of 4~6 hours, depending on the particular study. At all but the baseline interview, they are questioned to determine their percent relief from initial pain. Relief is coded on a 4-point

scale : 0=no relief ; 1=25% relief ; 2=50% relief ; 3=75% relief ; and 4=100% relief. In earlier studies, a point scale was used : 0=no relief ; 1=more than 50% relief. If the patient's pain is not sufficiently relieved to enable him to withstand a waiting period of 3 hours, he is medicated with conventional analgesics and removed from the study. On the other hand, if he could wait 3 hours or more and then requires additional medication, a conventional analgesic is administered and the score at the time of remedication is used for the remaining observations. Data are recorded on the attached analgesic data card and contain, in addition to hourly readings : information on side effects, when observed or volunteered ; the time after meals when the medication was given ; and the patient's age, pain site, and pain type. The statistical analyses of these data are carried out by a bioassay computer program. All calculations are done separately for the variables listed below :

Pain 0	Initial pain score (which must be either 2 or 3) at time of drug administration
Pain i	Pain intensity score at ith observation period (i=1,2,3,4,5,6,7)
SPID	Sum of the Pain Intensity Differences across time. It is derived by subtracting the pain score at each observation from the initial pain level. These individual pain-intensity-difference scores, weighted by the length of time since the preceding observation, are then added together, giving the SPID.
Relief i	The relief score at the ith observation period were (i=1,2,3,4,5,6,7)
TOTAL	The sum of the relief score weighted by the length of time since the

preceding observation are then added together giving total relief score.

The analyses includes a calculation of the means, estimates of the slope and intercepts of the dose-response curves were appropriate estimates of the relative potency with confidence curves, and analysis of variance including tests for linearity, parallelism, and pairwise t tests and a Tukey test¹⁾. If multiple dose studies are not performed, then the computer program eliminates those calculations which are related to a dose response bioassay.

Data collection is performed by a full time research nurse, who is specially trained for analgesic studies and whose commitment and responsibilities are to the investigator. We do not use nurses who are involved or responsible for patient care. The type of study designed may be a single dose comparison of a standard drug, a test drug and a placebo or a more complex design, in which we are interested in drug interaction or the addition of one drug to another, or multiple dose response studies.

Recently, several investigators²⁾³⁾ have utilized an incomplete block design, which was first described by Rerrup. In this design, each patient received the upper dose of one study drug and a lower dose of the other, on separate days. A group of 4 patients represent a cross-over block, balanced for drug, dose and order. To maintain this balance, it is necessary to substitute patients for those who fail to complete the study (Table 1). These investigators³⁾ have utilized a system of sequential related experiments, an appropriate end point for decision making after every block of 4 patients. For example, if the sum of the total scores in the 4 patients were greater for the standard drug than for the test drug, a decision to

Table 1 A Sample Block Design for a Twin Crossover Assay^a

Patient	Standard drug		Test drug	
	Lower dose	Upper dose	Lower dose	Upper dose
A	1 ^b			2
B		2	1	
C		1	2	
D	2			1

a : Selected from an assay containing several randomized blocks.

b : Numbers denote order of administration.

employ higher doses of a test drug would be made.

The sensitivity of the study varies with the observer, her training and experience. It is usually not difficult to obtain differences between placebo and the commonly used oral analgesic drugs. Significant graded dose effect curves with oral analgesics are most difficult and require a well trained nurse observer. If properly performed, this study yields the most information and permits the most accurate estimates of relative potency. The parenteral studies, because the medication is more potent, usually are easier to perform. The sample size required for oral analgesics is approximately 25~30 patients per treatment and a smaller sample size of 20 patients for the parenteral medication. Some investigators have stated they can use smaller sample sizes in their cross-over designs, but this has not been our experience.

I would like to illustrate some of the different study methods by showing you the results of our work which goes back for the past 17 years.

RESULTS

Fig. 1 is a comparison of equimolar amounts of propoxyphene hydrochloride and napsylate.

The means for the pain intensity scores are plotted in Fig. 1. Pain at 0 hour varied between 2.67 and 2.81 for the 7 treatments, but this difference was not significant. The mean maximum reduction in pain intensity was reached between 2 and 3 hours for all groups except placebo. Each of the equivalent dose groups (i.e., the same amount of base) showed greater efficacy with the napsylate salt than with the hydrochloride. Similarly, more relief was indicated with the napsylate salt than with comparable dose levels of the hydrochloride salt by mean values for pain intensity difference (Fig.

Fig. 1 Mean pain intensity scores (3=severe, 2=moderate, 1=slight) observed in patients treated with equimolar amounts of propoxyphene salts (HCL=hydrochloride, Naps=napsylate) and plotted for each observation period. N=number of subjects.

2), 50% relief (Fig. 3) and the summary variables SPID and Total. Pairwise t tests between equivalent dose levels revealed significant differences for SPID only between the 2 low doses, hydrochloride, 32 mg, and napsylate, 50 mg. Dose-response curves for propoxyphene hydrochloride and propoxyphene napsylate were obtained for all the variables and are illustrated for SPID and Total. (Fig. 4,5) These curves were constructed without assuming parallelism for both drugs (the lines were fit by least squares separately for each drug). Parallelism was as-

Fig. 2 Mean pain-intensity-difference scores observed in patients treated with propoxyphene salts (HCL=hydrochloride, Naps=napsylate). The scores are calculated by subtracting the mean pain intensity score for each observation point from the pain intensity at the 0 hr. N=number of subjects.

Fig. 3 Percentage of patients with 50% or more relief at each observation time after treatment with propoxyphene salts (HCL=hydrochloride, Naps=napsylate). N=number of subjects.

sumed in the calculation of relative potency. This assumption was tested in the analysis of variance and is, for these data, highly plausible. As can be appreciated visually, the fit is excellent.

The estimates of relative potency of the napsylate to the hydrochloride were 1.25 with a 99% confidence interval of 0.91~1.78 for SPID and 1.49 with a 99% confidence interval of 1.02~2.39 for the Total. Thus the estimates for these 2 parameters, which are indications of overall effectiveness, imply that the napsylate salt is more effective than the hydrochloride,

Fig. 4 Parallel line regression curves for SPID (sum of pain intensity difference) based on mg of propoxyphene base. HCL=hydrochloride, Naps=napsylate.

based on the mg of the propoxyphene base. It would require 125% to 149% of the propoxyphene base as hydrochloride to give the same analgesic effect as 100% of the napsylate.

The propoxyphene study was also designed to study the influence of previous medication on the response to a second test medication. In this study⁵⁾, all patients received placebo as a second administration. The bar graph, Fig. 6, illustrates that there is a relationship between what the patient received on the first day and the response to placebo on the second day. This points out the necessity in cross-over studies of carefully evaluating for order effect and the effect of previous study medication on responses.

In another study⁶⁾, Fig. 7, morphine was compared to a new analgesic, nefopam. Both drugs

Fig. 5 Parallel line regression curves for Total (total hours of 50% relief) calculated on mg of propoxyphene base. HCl=hydrochloride, Naps=napsylate.

were given intramuscularly. Nefopam is a new analgesic under investigation for a variety of painful clinical and experimental conditions. Chemically it is 5-methyl-1-phenyl-3, 4, 5, 6-tetrahydro-1H-2, 5-benzoxazocine hydrochloride. It is not classified with any other known analgesics because beyond its ability to relieve pain, nefopam shares no pharmacologic actions with other analgesics; it is not a CNS-depressant like morphine and its congeners; indeed, neurologic studies have shown enhanced reflex activity in man; and unlike aspirin, it has no anti-inflammatory or anti-pyretic effects. It appears to be a promising new analgesic.

The time-effect curves at the high and low dose were similar for nefopam and morphine (Fig. 7). The mean peak effect of nefopam 20 mg and of morphine 12 mg occurred at one

Fig. 6 SPID and Total scores for patients who received propoxyphene napsylate (PN) or hydrochloride (PH) as first medication and placebo (PL) as second medication.

hour. There was a tendency for both the low and high dose curves of both drugs, respectively, to remain juxtaposed over time. SPID values revealed a significant dose-response for nefopam (means : 6.1 and 8.7) and for morphine (means : 6.6 and 8.6) with the higher doses of each drug inducing greater analgesia. An estimate of the relative potency of nefopam to morphine was found to be 0.56 with a 95% confidence interval of 0.23 to 1.13, (Fig. 8). The combined analysis of variance revealed a significant regression and no significant deviation from parallelism. There was no significant difference between preparations averaged across both doses.

CONCLUSION

Utilizing the techniques described, it is pos-

Fig. 7 Mean pain intensity scores in patients treated with nefopam hydrochloride and morphine sulfate (each at 2 dose levels).

sible to evaluate both oral and parenteral analgesics, to obtain time-effect curves and to obtain limited information as to adverse effects. Adverse effects require larger sample sizes that are necessary to determine analgesic efficacy. The results are reproducible. Estimate of relative potencies may vary from one investigator to another, but usually are in reasonable agreement. The following basic principles of experimental design have been discussed:

1. Double Blind Technique
2. Use of Placebo
3. Use of Standard
4. Randomization as well as stratification of variables which are known to influence the results. Single dose vs. cross-over design.
5. Statistical validation

Analgesic studies are extremely time con-

Fig. 8 Parallel line regression curves for SPID (sum of pain intensity difference) based on mg of drug base.

suming and further refinement in methodology will be forthcoming as we learn more about how to manipulate psychological variables and how blood and other body fluid drug levels correlate which analgesic activity. The application of pharmacokinetics to clinical trials is an area under exploration. In the future, as we learn more about the endogenous opiate peptides and multiple endogenous agonists, new pharmacological approaches to pain relief will be developed and applied to mankind with the help of the clinical pharmacologist.

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討

山本(金沢大・医・麻酔)：お話しにありました nefopam という薬について、私ははじめておききましたのですが、静注が可能かどうかということと、pentazocine との比較を教えてくださいたいと思います。

Sunshine : The only clinical trials that I know of with nefopam have been used intramuscularly or orally. I believe, some people have used it intravenously, but it's under special situations. And I am not aware of its comparison to pentazocine. I did not compare. It might be available, but I do not have the information.

Sakuma (Tokyo Medical and Dental Univ.) : As you may know, in Japan such nice nurses are not available who will be in charge of the interview of the patient. In our case, are there any alternative suggestions according to your experience?

Sunshine : Yes, the only alternative would be the visual analogue scale by the patient. In other words, I said in my paper that we did

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not find the visual analogue scale of any advantage over the nurse interviewer, but what I could have also said is that it is just as good. So that I would think you can have the patients score themselves, and you would get more meaningful data than if you had individuals who had many other jobs to do and run study. But I would rather just instruct the patients to mark it themselves and to score themselves. And as a matter of fact, in dental pain, one of the investigators has sent the patient home with a scale, and the next day, the patient mails the form in. And they have been able to do dose-response work. So, I think that would be the way to overcome the problem.

Sakuma : Better than the doctors do?

Sunshine : I think so. I think doctor doing the study would add everything would look like everything else, and all you would do, is to get the doctors opinion as to what he thought was the best drug.