Drug development involves the chemical identification and characterization of a compound to determine stability and define the drug’s preliminary actions. Preclinical research follows in animals to develop a pharmacokinetic profile to determine dose range, biotransformation, elimination, and toxicology. The 4 phases of clinical research, phase 1 to phase 4, encompass a progressive investigation of healthy subjects, otherwise healthy patients, to patients with a target disease to obtain US Food and Drug Administration (FDA) approval. Clinical studies include open-label noncomparative studies during phases 1 and 2, and double-blind, comparative, and placebo-controlled studies during phases 2 and 3. Approval from the FDA follows the successful evaluation of the drug. After drug marketing, phase 4 clinical trials continue to collect safety and efficacy information.

Many drugs that undergo this drug development process succeed in obtaining FDA approval and are marketed for clinical use. There are several circumstances, however, that preclude the successful completion of drug development, FDA approval, and marketing. This study describes a clinical trial of a new benzodiazepine, Ro 48-6791. Ro 48-6791 was being developed as an ultra-short-acting benzodiazepine with clinical effects of shorter duration than midazolam. The purpose of this study was to define a safe dose range for the induction and maintenance of conscious sedation of patients in an outpatient gastroenterology laboratory. Efficacy criteria to be evaluated included time to onset of action, duration of action, and psychomotor fitness upon recovery. Patients were assessed by using the Observer’s Assessment of Alertness/Sedation score (OAA/S) and a 5-m heel-toe-line-walk test (HTLW).

The patients were divided into 2 groups. Group 1 patients received Ro 48-6791. Group 2 patients were premedicated with meperidine before administration of Ro 48-6791. Ro 48-6791 was titrated over 30 seconds, and patients were observed for 90 seconds before the next dose was given. The OAA/S score, oxygen saturation, and vital signs were charted every minute through induction and every 5 minutes during the procedure. Patients received Ro 48-6791 until they reached an OAA/S score of 3, corresponding to slowed patient response to name calling.

Group 1 (Ro 48-6791 alone) required greater induction doses and increased time to induction. Maintenance doses were the same for both groups. The duration of action of Ro 48-6791 as measured by the
OAA/S score and HTLW test did not differ between groups.

Ro 48-6791 seemed to be a safe and effective agent to achieve conscious sedation in outpatients undergoing short invasive procedures. However, clinical drug development of Ro 48-6791 was stopped because it did not meet the efficacy criteria of an ultra-short-acting benzodiazepine.

Key words: Benzodiazepines, drug development, efficacy, US Food and Drug Administration (FDA), phase 1 through 4 clinical trials, pharmacokinetics.

Introduction

The research and development of new pharmacologic agents is an ongoing commitment of pharmaceutical companies. Drug discovery generally occurs after the chemical synthesis of a compound. Plants, animal sources, genetic engineering, and synthetic compounds serve as possible precursors in the development of a drug. Computer modeling of the chemical structure of a compound provides structure-activity relationship information. Chemical and biological characterization of the compound will determine stability, physical characteristics such as the freezing and boiling points, and preliminary actions. Preclinical research continues in animals with the development of a pharmacokinetic profile detailing the subtherapeutic, therapeutic, and toxic doses, half-life, means of biotransformation and elimination, and toxicology. When significant safety data are attained, the compound seems effective, and a dosing regimen is determined, preclinical research transitions to clinical research in humans. At this time, the pharmaceutical company submits the accumulated data to the US Food and Drug Administration (FDA) for an investigational new drug application.1

There are 4 phases of clinical research, phase 1 to phase 4, that are essential to the drug development process (Figure). Phase 1 trials are done in healthy subjects to obtain information on tolerance to the drug and additional pharmacokinetic data. These trials are designed as open-label non-comparative studies in which the researcher and patient are aware that only the study drug is being administered. Following this, phase 2 trials are conducted. In phase 2 trials, the drug is administered to otherwise healthy patients according to a rigid protocol design to determine drug efficacy, bioavailability, and a dose-response relationship.

Double-blinded and comparative studies (the patient and the researcher are unaware of which drug is being given) or placebo-controlled (neutral substances with no clinical activity) studies are introduced during this phase in addition to open-label drug studies. Phase 3 trials are generally large multicentered studies in which phase 2 information is confirmed and expanded to patients at higher risk. Patient safety is of the highest priority. Approval from the FDA depends on statistically significant data obtained to determine the safety, efficacy, pharmacokinetic profile, site of action, and adverse effects during phase 2 and 3 trials of the study drug. After FDA approval and drug marketing, phase 4 trials continue with the collection of safety information in the use of the new drug now available to clinicians. During clinical trials, adverse effects must be reported to the drug company sponsoring the study, and extensive data are kept in the case report form.1

What happens when following these prescribed steps the drug fails to meet expectations? During an open-label noncomparative pilot study, phase 2 trial involving a new water-soluble benzodiazepine, Ro 48-6791 (Tempium; Hoffmann-LaRoche, Nutley, NJ), the trial was halted by the pharmaceutical company. This potentially new class

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**Figure.** The drug development process

The discovery and characterization of a compound initiates a series of prescribed steps to develop the drug for the clinical market. After successful preclinical trials, an investigational new drug (IND) application is submitted by the pharmaceutical company to the US Food and Drug Administration (FDA). Clinical research (phases 1-3) are conducted, and the data are submitted to the FDA to obtain market approval. Courtesy of Ruth Ann Nylen, PhD (copyright 1994).
of benzodiazepines, short-acting intravenous sedatives, was to impart a clinically and significantly shorter recovery time. Initial chemical studies found Ro 48-6791 to have similar pharmacokinetic and pharmacodynamic actions as midazolam, but Ro 48-6791 displayed a shorter and more predictable duration of action than midazolam. It binds to the receptor ligand at the benzodiazepine receptor, located on the a subunit of the g-aminobutyric acid receptor in the central nervous system, displaying full agonist activity resulting in sedative, myorelaxant, and amnestic effects in animals. The phase 1 clinical pharmacology studies suggested that Ro 48-6791 is 4 times as potent as midazolam when given to healthy nonelderly men and displays a shorter and more predictable duration of action. In clinical pharmacology studies in healthy volunteers with a wide range of ages, there was no evidence of major effects on cardiac or respiratory function. The greater sedative-hypnotic potency, shorter duration of action, and faster recovery of Ro 48-6791 than midazolam suggested it would be an ideal new benzodiazepine useful in anesthesia for sedation, induction, and maintenance purposes. Phase 2 clinical trials on Ro 48-6791 were instituted.

The primary objective of this pilot study was to determine the dose requirements of Ro 48-6791 for the induction and maintenance of conscious sedation in outpatients undergoing an invasive procedure. In addition, the safety profile of the dose regimen between different age groups and ASA classification was to be assessed. The study was conducted in a gastroenterology clinic on patients undergoing esophagoscopy, colonoscopy, or both. The reported short-acting pharmacologic characteristics of Ro 48-6791 suggested this drug to be of benefit for patients undergoing short procedures.

Methods

Approval for this study was granted by the institutional review board of a large metropolitan hospital. Informed consent was obtained from each patient before inclusion in the study. The patients chosen were scheduled for outpatient esophagoscopy, colonoscopy, or both in the gastroenterology laboratory. They were classified according to age and ASA classification of physical status. Patients were then divided into 2 groups:

*Group 1:* Patients were premedicated with Ro 48-6791. Meperidine was given as necessary following induction of conscious sedation with Ro 48-6791. Meperidine is the opioid commonly used in the gastroenterology laboratory.

*Group 2:* Patients were premedicated with meperidine (25-50 mg) followed by Ro 48-6791. Additional meperidine was given as needed during induction of conscious sedation and the procedure.

Ro 48-6791 was supplied by the pharmaceutical company in 15 mg/3 mL vials that were kept refrigerated. Just before use, a vial was diluted with sterile normal saline to a concentration of 0.25 mg/mL. The meperidine used was issued by the hospital’s pharmacy.

Patients were screened according to established inclusion and exclusion criteria. Patients who had taken benzodiazepines within 48 hours before they would have received the test drug and patients who had received benzodiazepines long term were excluded as part of the criteria. Other exclusion criteria included pregnancy, acute narrow-angle glaucoma, present drug- or alcohol-induced intoxication, a recipient of an investigational drug within the past 2 months, visual impairment or inability to perform the physical test for assessment of motor ability, dialysis-dependent renal failure, or hepatic failure secondary to portal hypertension or hepatic encephalopathy.

After informed consent was obtained, the history and physical examination were reviewed, vital signs were taken and recorded, blood was obtained for serum liver and renal function tests, and a 20-gauge intravenous catheter was inserted. A rapid urine pregnancy test was done on women of childbearing potential, and a “dipstick” urinalysis was checked for all patients’ (pH, specific gravity, glucose, ketones, blood, and protein were measured). Following verbal instructions and before any medications were given, patients completed a heel-toe-line-walk (HTLW) test. For this test, patients were instructed to walk carefully with one foot in front of the other, heels touching toes, for 5 m. Patients unable to complete the HTLW test within 60 seconds or after 3 attempts were not eligible for the study. The total cumulative time to complete the HTLW test was noted as a baseline value. In addition, patients were assessed using an Observer’s Assessment of Alertness/Sedation score (OAA/S) (Table 1). During the procedure, the lowest acceptable limit of sedation for this study was an OAA/S score of 3. This level of sedation is typified as patients responding only when their name is called loudly or repeatedly. An OAA/S score less than 3 was considered oversedation.

Before each procedure, routine monitors (electrocardiograph, pulse oximetry, and blood...
pressure cuff) were applied. In group 1, patients received Ro 48-6791 only for induction, meperidine was given when necessary during the procedure; group 2 patients were premedicated with meperidine before administration of Ro 48-6791, and additional meperidine was given during the procedure when necessary. Ro 48-6791 was always given over 30 seconds, followed by a patient observation of 90 seconds before the administration of additional Ro 48-6791. The OAA/S score, oxygen saturation, and vital signs were charted every minute through induction and every 5 minutes during the procedure. Initial doses of Ro 48-6791 were given according to patient’s age and ASA classification. Dosage increments of 0.25 to 0.5 mg of Ro 48-6791 were used to sedate patients to an OAA/S score of 3 for induction, then maintained at that level with additional dose increments of 0.5 to 1.0 mg for the procedure.

At the end of the procedure, defined as removal of the endoscope, the OAA/S score was assessed every 5 minutes until the patients reached a score of 5. At that time, the HTLW test was attempted. If needed (ie, the patient was dizzy while walking), the HTLW test was repeated every 15 minutes until the patient successfully completed the HTLW test to a test value within 1 second of the baseline value. Once successful, the patient was considered to have fully recovered psychomotor function. The patient was discharged after the completed tests, according to policies for conscious sedation in the gastroenterology laboratory.

Each patient was contacted 24 hours after the procedure. The patients were queried regarding recall of the procedure and any side effects.

### Results

A total of 72 outpatients were enrolled in the study; 14 patients were disqualified because of inability to complete the HTLW test. Data were collected on the 58 patients able to complete the study. Patients were divided into groups by age, ASA status, and premedication. Ro 48-6791 was titrated to assess the sedative effects, determine dose, and to maintain the safety of the patient.

Mean induction doses of Ro 48-6791 were recorded with corresponding recovery times (Table 2). The mean induction dose of Ro 48-6791 was doubled in all groups of patients when this medication was the sole induction agent (group 1 mean induction dose, 2.77 mg; group 2 mean induction dose, 1.38 mg). The maintenance dose of Ro 48-6791 used during the procedure was the same for groups 1 and 2. The total meperidine dose (47.5 mg) was similar between the groups.

Induction time necessary to reach an OAA/S score of 3 was greater when Ro 48-6791 was used as the sole induction agent in group 1 (7.8 minutes). When meperidine was given before Ro 48-6791 in group 2, the time needed to reach an OAA/S scale of 3 was less (5.3 minutes) (see Table 2).

The mean recovery time to an OAA/S scale of 5 for group 1 was 15 minutes, and completion of the HTLW test was 27 minutes. In group 2, the

### Table 1. Observer’s Assessment of Alertness/Sedation Score (OAA/S)*

<table>
<thead>
<tr>
<th>Patient response</th>
<th>Speech</th>
<th>Facial expression</th>
<th>Eyes</th>
<th>Composite score (level of sedation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responds readily to name spoken in normal tone</td>
<td>Normal</td>
<td>Normal</td>
<td>Clear, no ptosis</td>
<td>5 (alert)</td>
</tr>
<tr>
<td>Lethargic response to name spoken in normal tone</td>
<td>Mild slowing or thickening</td>
<td>Mild relaxation</td>
<td>Glazed or mild ptosis (less than one half the eye)</td>
<td>4</td>
</tr>
<tr>
<td>Responds only after name is called loudly and/or repeatedly</td>
<td>Slurring or prominent slowing</td>
<td>Marked relaxation (slack jaw)</td>
<td>Glazed and marked ptosis (more than one half the eye)</td>
<td>3</td>
</tr>
<tr>
<td>Responds only after mild prodding or shaking</td>
<td>Few recognizable words</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Does not respond to mild prodding or shaking</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 (deep sleep)</td>
</tr>
</tbody>
</table>

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mean recovery time to an OAA/S scale of 5 was 12.8 minutes, and the time to completion of the HTLW test was 24 minutes (see Table 2).

Of 58 patients, 48 were reached by telephone 24 hours after the procedure for follow-up assessment. Fourteen patients (29%) complained of drowsiness, and 2 patients (4%) had hiccups during and after the procedure. No patient recalled the procedure from approximately the time of injection to approximately 15 to 30 minutes after the procedure. Nausea was a complaint of 4 patients (8%), but these patients also received meperidine; therefore, the causative agent was difficult to determine.

Discussion

Ro 48-6791 seemed to be a safe and effective agent to perform conscious sedation without respiratory or cardiovascular depression in outpatients undergoing short gastrointestinal endoscopic procedures. When combined with meperidine, the total Ro 48-6791 dose was lower because of the additive effect of the narcotic. The endoscopic procedures performed on these patients were stimulating, uncomfortable, and, at times, painful. It was apparent that a narcotic was a necessary pharmacologic component for successful sedation.

Enrollment in the present study began with patients younger than 65 years of age with an ASA classification of I or II to determine the effective dose range. A secondary objective of the present study was to evaluate the safety profile using Ro 48-6791 in elderly or debilitated patients. This information then was used for dosing in older, more debilitated patients. The findings showed the initial doses of Ro 48-6791 did not need to be adjusted, but the rate of titration required was slower for older patients. There was transient hypotension observed in the older group immediately after injection of Ro 48-6791, but it was self-limiting or resolved quickly with verbal or tactile stimulation and/or intravenous fluids. The use of meperidine along with Ro 48-6791 decreased the overall Ro 48-6791 dose requirements, but overall drug requirements were similar between the 2 age groups. It is suggested that Ro 48-6791, when titrated slowly, could be used safely for elderly or debilitated patients.

Fewer than 30% of the patients reported adverse events after endoscopy, with no significant difference reported between the 2 groups. The adverse events reported included hiccups, abdominal pain, drowsiness, nausea, flatulence, and headache. All adverse events were of mild intensity and not considered to be related solely to Ro 48-6791 administration, indicating Ro 48-6791 has an acceptable safety index.

The initial protocol required the patient’s level of sedation from Ro 48-6791 to reach a level of 3 on the OAA/S scale. The average Ro 48-6791 dose requirement necessary for a sedation level of 3 was 2.77 mg. However, during the course of the clinical trial, it was noted by the anesthesia team and the gastroenterologist performing the procedure that patient sedation to an OAA/S score of 3 was unnecessary for induction of conscious sedation for endoscopy. A protocol revision was made to change the requirement for induction OAA/S score to 4 instead of 3. With this revised protocol, Ro 48-6791 could be given when necessary during the procedure to maintain an OAA/S sedation score of 4. This resulted in lower total doses of Ro 48-6791 given, which improved the time to overall patient recovery from psychomotor impairment as determined by the OAA/S scores and completion of HTLW motor tests. When an OAA/S level of 4 was believed sufficient for initial sedation, the time of onset of action time was decreased (3.0 ± 1.3 minutes, Ro 48-6791 alone; 2.7 ± 1.3 minutes, Ro 48-6791 and meperidine).

The duration of action of Ro 48-6791 was measured by the patients’ recovery from psychomotor impairment. Initial recovery time was

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean induction doses of Ro 48-6791 (mg)</th>
<th>Mean induction times (min)</th>
<th>Recovery to OAA/S* of 5 (min)</th>
<th>Recovery to HTLW* test (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 25)</td>
<td>2.77</td>
<td>7.8</td>
<td>15.0</td>
<td>27</td>
</tr>
<tr>
<td>2 (n = 33)</td>
<td>1.38</td>
<td>5.3</td>
<td>12.8</td>
<td>24</td>
</tr>
</tbody>
</table>

*OAA/S indicates Observer’s Assessment of Alertness/Sedation score; HTLW indicates heel-toe line walk.
recorded from the end of the procedure to the return to an OAA/S score of 5. In the present study, the time to recovery was similar in both groups. At the end of the procedure, patients in both groups were able to respond to commands and were transferred to the recovery area immediately. This level of awareness following Ro 48-6791 administration was unique to this benzodiazepine. When compared with midazolam, both Ro 48-6791 groups required less time to return to an OAA/S score of 5. The second phase of recovery, defined as return of psychomotor function, was measured from the end of the procedure to return to the baseline HTLW value. The recovery time to this parameter also was similar between groups but was only slightly more rapid than the recovery time to baseline HTLW value for midazolam.

Phase 1 (preclinical) data indicated that Ro 48-6791 was 4 times as potent as midazolam, and its recovery time was reduced consistently compared with that for midazolam. A total of 4 phase 2 trials were designed based on this preclinical information, including the present study. A coincident double-blind study of Ro 48-6791 vs midazolam, each given by intravenous infusion for the induction and maintenance of conscious sedation, was developed to determine the necessary induction dose of Ro 48-6791. The results of the study showed Ro 48-6791 to be only twice as potent as midazolam, and when the 2 drugs were given in equipotent doses, the primary recovery milestone (time to ambulation) was no different between the Ro 48-6791 and midazolam groups.

Still another study evaluated the potency of Ro 48-6791 compared with midazolam when used as coinduction agents with propofol. This study was double-blinded and compared Ro 48-6791 with midazolam and placebo. The results showed the shortest recovery time to be the placebo group. Comparisons between midazolam and Ro 48-6791 showed midazolam to have a shorter recovery in the intermediate dose range. Also at this dose range, midazolam had more pronounced anxiolytic and amnestic effects over Ro 48-6791, even at a lower propofol dose.

In a third study, when Ro 48-6791 was compared with propofol for induction of general anesthesia, the safety profile of Ro 48-6791 compared with propofol (mean apnea duration of 45 seconds vs 200 seconds, respectively), was significant; however, the recovery was as slow as expected for midazolam and approximately twice as long as propofol. The most likely explanation for the results of these 3 studies is the initial overestimation of the potency ratio based on the phase 1 data.

In the present study, Ro 48-6791 was an effective and safe drug for conscious sedation in young, elderly, and debilitated patients. Given the stimulating nature of these endoscopic procedures, meperidine was used in conjunction with Ro 48-6791 for sedation and pain relief. Initial dosing parameters based on a potency ratio of 1:4 with midazolam were not considered accurate, but a 1:2 potency ratio seemed to be more accurate. The onset of action measured by the OAA/S score of 3 was of relatively short duration, and patient recovery and transfer to the recovery area was rapid. The time to full recovery to an OAA/S score of 5 and successful completion of the HTLW test also was short, and none of the patients had a delay in discharge resulting from the study medication. However, despite the rapid onset of action and recovery from Ro 48-6791, it was not substantially faster than the recovery observed with midazolam. The initial projection for Ro 48-6791 stated by the manufacturer was a 50% reduction in midazolam recovery time. It did not seem that this study medication met that reduction in recovery time or had a significant advantage over midazolam.

Why did this drug trial fail? This benzodiazepine, Ro 48-6791, is an efficacious sedative useful for conscious sedation. This drug has a quick onset of action, offers a predictable and rapid recovery profile, and is devoid of significant cardiovascular or respiratory adverse effects, but it does not provide a unique alternative to the existing benzodiazepine, midazolam. Three reasons are identified to be responsible for the decision to stop further study of Ro 48-6791:

1. **Potency.** The initial pharmacodynamic data indicating Ro 48-6791 was 4 times as potent as midazolam were soon discovered to be inaccurate when dosing the first patients in this study. Given this potency ratio, the investigators assumed that the average dose necessary to achieve conscious sedation in the study patients would be 0.25 mg to 1 mg. The average dose necessary to achieve conscious sedation in this study was 2.77 mg. This dose was decreased to 1.38 mg when meperidine was coadministered for induction of conscious sedation. If Ro 48-6791 were 4 times as potent as midazolam, the pharmaceutical company would have formulated Ro 48-6791 in a concentration of 0.25 mg/mL. As a result of the present study and the 3 coincident studies this concentration of Ro 48-6791 was not possible; the concentration...
most likely would have been 1 mg/mL, which is identical to the midazolam concentration.

2. Reduction in recovery from psychomotor impairment. Initial preclinical phase 1 trials suggested Ro 48-6791 had a significant reduction in the time to recovery compared with midazolam. However, in the present study and the 2 coincident well-controlled double-blind studies comparing Ro 48-6791 and midazolam, this significant reduction in recovery time was not duplicated. The study was discontinued as a result of the failure of Ro 48-6791 to meet an efficacy criterion of about 50% clinical reduction in recovery time from midazolam. It must be noted that although the time to successful completion of the HTLW test in the present study did not yield a significant reduction in recovery time, clinically, the patients appeared alert and oriented. When questioned 24 hours later, patients stated they were pleased with the drug's performance and felt no hangover sedative effects after the procedure.

3. Economics. “Is there a clinical need for another benzodiazepine?” The two currently available benzodiazepines used in anesthesia, diazepam and midazolam, enjoy widespread use. They are both effective sedatives used for preoperative anxiety, induction, maintenance, and in the recovery phase of an anesthetic. Diazepam has been used in clinical practice since the 1950s, and when midazolam was introduced in the mid-1980s, it possessed pharmacologic qualities superior to those of diazepam. Midazolam is water-soluble, does not cause pain on injection, and has a shorter onset of action and recovery time than diazepam. In clinically effective doses, neither drug depresses the cardiovascular or respiratory systems. Even if Ro 48-6791 had a more significant reduction in recovery time, it was not apparent that this drug offered a clinical advantage over midazolam. The cost of drug development and marketing would have made the purchase price of Ro 48-6791 greater than that of midazolam, affecting the ability of most institutions to justify its use.

New drug development and improving drug safety is important to the clinical practitioner. The research and development of drugs by pharmaceutical companies have been responsible for newer, safer agents causing major medical breakthroughs. The anesthesia provider should attempt to become involved in clinical trials in an effort to improve clinical practice and, at the same time, recognize that new drug products should offer a distinct advantage over existing drugs to be able to justify their use economically. Ro 48-6791 was a safe, effective benzodiazepine. In all the chemical studies and in the initial preclinical phase 1 trials, it seemed to offer a significant reduction in recovery time compared with midazolam. If this had continued to be demonstrated in other clinical studies, Ro 48-6791 would have been the prototype for the short-acting intravenous sedatives class of benzodiazepines. The next step would have been to determine whether this reduction in recovery time enhanced patient care and was cost-effective. Clinical trials leading to FDA approval are a slow but necessary process for the development and ultimate marketing of a safe and effective product.

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