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# Safety Assessment of the Use of Perflenapent Emulsion for Contrast Enhancement of Echocardiography and Diagnostic Radiology Ultrasound Studies

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**Summary**

*Purpose:* The studies were undertaken to assess the safety of the use of perflenapent emulsion (EchoGen®, SONUS Pharmaceuticals, Bothell, Wash.) for contrast enhancement of echocardiography and radiology ultrasound studies.

*Materials and methods:* In all, 1,001 patients or subjects were enrolled in 21 clinical studies. Clinical laboratory tests, pulse oximetry, vital signs, and electrocardiograms (ECGs) were obtained in 818 patients before and after administration of perflenapent emulsion and active control [5% sonicated human albumin, (Albunex®, Molecular Biosystems, Inc., San Diego, Calif.)] or placebo (saline) to determine mean changes from baseline. Adverse event rates were monitored following administration of perflenapent emulsion in 743 patients and placebo in 151 patients.

*Results:* No clinically significant abnormalities in clinical laboratory, pulse oximetry, vital signs, or ECG evaluations were observed. Values following administration of perflenapent emulsion were comparable with those following placebo or active control. Perflenapent emulsion (50/743; 6.7%) was comparable with placebo (4/151; 2.6%) in the overall incidence of adverse events considered related to the test article. Adverse events that occurred with a frequency of ≥1% within 30 min after perflenapent emulsion administration were vasodilation and taste aberration. Adverse events which were mostly mild to moderate in intensity, began within 10 to 20 min after administration, and resolved spontaneously within 10 to 20 min.

*Conclusion:* Perflenapent emulsion is generally well tolerated in patients undergoing echocardiography and ultrasound of other target organs.

**Key words:** contrast agent, safety, EchoGen®, adverse effects, perflenapent emulsion

## Introduction

The ability of contrast agents to increase the efficacy of ultrasound and Doppler examinations has grown during the last 20 years. The ideal contrast agent would be a nontoxic, ready-to-use formulation, injectable intravenously, capable of crossing the pulmonary capillary bed, stable enough for the duration of the ultrasound examination, and would provide both Doppler and gray-scale enhancement.[1]

A new class of ultrasound contrast agents fulfills most of these criteria. Perflenapent emulsion (EchoGen®, SONUS Pharmaceuticals, Bothell, Wash.) is a patented[2] phase shift (liquid-in-liquid) emulsion that contains a liquid, dodecafluoropentane (DDFP, boiling point 29.3°C), as the dispersed phase. DDFP is converted to gaseous microbubbles by hypobaric activation just prior to administration. The microbubbles circulate within the intravascular space and provide strong backscatter during ultrasound imaging. These microbubbles are small enough to cross the lung capillary bed, yet they persist in solution much longer than do microbubbles of air, carbon dioxide, or other gases of similar size.

Perflenapent emulsion is not metabolized but is excreted via the lungs.[1] Clinical studies have demonstrated that perflenapent emulsion provides prolonged contrast enhancement in echocardiography and radiology studies of kidney, liver, and vasculature.[3]

These studies assess the safety of perflenapent emulsion for use in echocardiography and radiology ultrasound studies of kidney, liver, and vasculature. In addition to assessing general safety, the battery of tests was designed to ensure monitoring

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of all possible toxic effects related to injection of perflenapent emulsion. Specifically:

- **Cardiovascular.** Because perflenapent emulsion is indicated for use in echocardiography for patients undergoing cardiac function evaluation, several tests were conducted to determine cardiac safety.
- **Pulmonary.** Because perflenapent microbubbles pass through the lungs and perflenapent is excreted unchanged via exhalation, tests were conducted to monitor pulmonary function. Adverse events that had a respiratory component were also monitored.
- **Renal.** X-ray contrast media produce frequent iatrogenic renal function impairment.[4-6] As such, an important aspect of the drug development of perflenapent emulsion was to determine whether this drug would be safe for those patients with renal problems.
- **Central nervous system.** To assess the impact of administration of perflenapent emulsion on nervous system function, an abbreviated cranial nerve assessment was performed in some patients. Adverse events of the nervous system were also monitored.
- **Immune.** Histamine, tryptase, and tumor necrosis factor were measured to monitor for possible anaphylaxis or anaphylactoid reaction to perflenapent emulsion.
- **Hematologic parameters.** As is routine for intravenous pharmaceuticals, certain hematologic parameters were measured.

## Materials and Methods

The tests and evaluations performed in these studies, organized by body system, are shown in Table I.

A total 1,001 patients or subjects were enrolled in 21 clinical studies. Four of these studies were phase III controlled clinical studies. Two controlled clinical studies were trials of facilitated contrast enhancement in diagnostic ultrasound of the liver, kidneys, or vasculature after administration of perflenapent emulsion (EchoGen®) versus placebo (saline). The other two controlled clinical studies were trials of facilitated contrast enhancement in echocardiography after administration of perflenapent emulsion versus active control (Albunex®).

Patients in early studies received a formulation of perflenapent emulsion that contained a surfactant not included in the final formulation. The final formulation was administered to 743 patients. Laboratory tests and vital signs are reported for both formulations. Adverse events are reported for those patients who received the final formulation.

TABLE I Summary of safety evaluations by body system

| | Healthy subjects | Patients |
|---|---|---|
| General health | | |
| Physical exam | X | |
| Adverse events | X | X |
| Discomfort | X | X |
| Temperature | X | X |
| Serum chemistry | X | X |
| Cardiovascular | | |
| Blood pressure | X | X |
| Heart rate | X | X |
| Cardiac function | X | |
| Segmental wall motion | X | X |
| Ejection fraction | X | |
| ECG | X | X |
| Pulmonary | | |
| Respiratory rate | X | X |
| Oximetry | X | |
| Pulmonary function spirometry | X | |
| Pneumotachometry | | X |
| Renal | | |
| Urine volume | X | |
| Urine creatinine | X | |
| Creatinine clearance | X | |
| Body surface area-adjusted creatinine clearance | X | |
| Urinalysis | X | X |
| Serum BUN | X | X |
| CNS | | |
| Comprehensive neuro | X | |
| Cranial nerve | X | X |
| Immune | | |
| Histamine | X | |
| Tryptase | X | |
| Tumor necrosis factor | | X |
| Hepatic | | |
| AST | X | |
| ALT | X | |
| GGT | X | |
| LDH | X | |
| Hematologic parameters | | |
| Blood coagulation | X | X |
| Prothrombin time | X | X |
| Activated partial thromboplastin time | X | X |
| Iron | X | X |
| Bilirubin | X | X |

*Abbreviations:* ECG = electrocardiogram, BUN = blood urea nitrogen, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = glutamyltransferase, LDH = lactose dehydrogenase.

### Demographics

The demographics of the controlled clinical studies and 13 clinical pharmacology studies are shown in Table II. In the four controlled clinical studies, 405 patients received perflenapent emulsion. Of these patients, 70.8% were male, 79.4% were white, 86.5% had medium or large body frames, and 61.2% were < 65 years of age. Of the 413 subjects enrolled in the clinical pharmacology studies, the majority were male (79.4%) and were white (74.8%). The subjects ranged in age from 17 to 92 years and 69.5% were < 65 years. Demographics for the additional 183 patients are not reported here.

TABLE II Patient demographic characteristics for controlled clinical studies

| Characteristics | Controlled clinical (n = 405) (%) | Clinical pharmacology (n = 413) (%) |
|---|---|---|
| Age (years) | | |
| Mean (SE) | 59.0 (0.7) | 52.5 (17.4) |
| Range | 21–94 | 17–92 |
| 17–49 | 102 (25.1) | 166 (40.2) |
| 50–64 | 147 (36.1) | 121 (29.3) |
| < 65 | 249 (61.2) | 287 (69.5) |
| ≥ 65 | 158 (38.8) | 126 (30.5) |
| Gender | | |
| Male | 288 (70.8) | 328 (79.4) |
| Female | 119 (29.2) | 85 (20.6) |
| Race | | |
| White | 323 (79.4) | 309 (74.8) |
| Black | 50 (12.3) | 59 (14.3) |
| Hispanic | 22 (5.4) | 33 (8.0) |
| Other | 12 (2.9) | 12 (2.9) |
| Body frame | | |
| Small | 55 (13.5) | 53 (14.3) |
| Medium | 226 (55.5) | 252 (67.9) |
| Large | 126 (31.0) | 66 (17.8) |

*Abbreviations:* n = Number of patients, SE = standard error.

### Studies

The order of events in the radiology and echocardiography studies is shown in Table III and Table IV, respectively. The radiology study was a double-blind, placebo-controlled study. Patients received 0.05 ml/kg perflenapent emulsion and 0.05 ml/kg saline (0.9% sodium chloride injection USP) in random order followed by ultrasound examination. The echocardiography studies were single-blind, active-controlled studies. Patients received 0.22 ml/kg active control and then 0.05 ml/kg perflenapent emulsion, each followed by ultrasound examination. Patients enrolled in the other studies received dosages of 0.01 to 0.35 ml/kg of perflenapent emulsion.

### Vital Signs and Laboratory Tests

Clinical laboratory tests performed and the times samples taken are shown in Table V. The parameters measured are listed in Table VI.

Vital signs and oxygen saturation were measured and electrocardiograms (ECGs) were recorded using normal hospital procedures. Baseline measurements were taken and measurements were made every 2 or 3 min for at least 15 min after injection. Follow-up measurements were taken at intervals that varied, depending on the study, from 24 to 120 h postinjection. Pulmonary function was measured by spirometry and pneumotachometry in a subset of patients at times shown in Table VII.

### Pulmonary Function

Pneumotachometry was performed in a subset of patients to measure tidal volume, respiratory rate, and minute ventilation. Using a Medigraphics CPX/D or Sensormedics 2900, baseline measurements were taken 5 min prior to injection of each agent. Measurements were taken at times shown in Table VII.

TABLE III Order of events in radiology studies

| | |
|---|---|
| Prestudy | Baseline blood, urine, ECG, and ultrasound |
| Pretest article 1[a] injection | Vital signs, oxygen saturation<br>Patient questioned "How do you feel?" |
| Test article 1 injection | |
| Posttest article 1 injection | Continuous ultrasound<br>Periodic measurement of vital signs, oxygen saturation, and ECG<br>Patient questioned about injection site discomfort and adverse events |
| Pretest article 2[a] injection | Baseline ultrasound<br>Vital signs and oxygen saturation<br>Patient questioned "How do you feel?" |
| Test article 2 injection | |
| Posttest article 2 injection | Continuous ultrasound<br>Periodic measurement of vital signs, oxygen saturation, and ECG<br>Patient questioned about injection site discomfort and adverse events |
| 1–2 h post injection | Blood and urine samples obtained |
| Follow-up (24–48 h) | Blood and urine samples obtained<br>Adverse events followed until an outcome is determined |

[a] Test articles 1 and 2 are perflenapent emulsion and placebo (saline) given in random order.
*Abbreviation*: ECG = electrocardiogram.

TABLE IV Order of events in echocardiography studies

| | |
|---|---|
| Prestudy | Baseline blood, urine, ECG, and echocardiograph |
| Preactive control injection | Vital signs, oxygen saturation<br>Patient questioned "How do you feel?" |
| Active control injection | |
| Postactive control injection | Continuous echocardiogram<br>Periodic measurement of vital signs, oxygen saturation, and ECG<br>Patient questioned about injection site discomfort and adverse events |
| Preperflenapent emulsion injection | Baseline echocardiogram<br>Vital signs and oxygen saturation<br>Patient asked "How do you feel?" |
| Perflenapent emulsion injection | |
| Postperflenapent emulsion injection | Continuous echocardiogram<br>Periodic measurement of vital signs, oxygen saturation, and ECG<br>Patient questioned about injection site discomfort and adverse events |
| 1–2 h follow-up | Blood samples obtained |
| Follow up (24–48 h) | Clinical evaluation and questioning about adverse events |

*Abbreviation:* ECG = electrocardiogram.

Table V Summary of laboratory tests in subjects/patients receiving perflenapent emulsion

| | Baseline | 1 h | +1–2 h | 2 h | +3 h | +8 h | 12 h | +24 h | 36 h | +24–48 h | +48 h | +72 h | +96 h | +120 h |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Routine labs | | | | | | | | | | | | | | |
| Serum chemistry | 754 | 61 | 427 | 200 | 22 | 25 | 0 | 54 | 0 | 633 | 152 | 54 | 29 | 0 |
| Hematology | 740 | 64 | 422 | 196 | 22 | 24 | 0 | 54 | 0 | 625 | 147 | 54 | 29 | 0 |
| Urinalysis | 295 | 0 | 148 | 100 | 0 | 0 | 0 | 54 | 0 | 225 | 154 | 54 | 29 | 0 |
| Liver function | | | | | | | | | | | | | | |
| AST | 750 | 62 | 425 | 199 | 22 | 25 | 0 | 54 | 0 | 631 | 54 | 54 | 29 | 0 |
| ALT | 748 | 62 | 425 | 199 | 22 | 25 | 0 | 54 | 0 | 631 | 54 | 54 | 29 | 0 |
| GGT | 745 | 62 | 427 | 199 | 22 | 25 | 0 | 54 | 0 | 633 | 54 | 54 | 29 | 0 |
| LDH | 716 | 62 | 379 | 192 | 22 | 25 | 0 | 54 | 0 | 622 | 54 | 54 | 29 | 0 |
| Special tests | | | | | | | | | | | | | | |
| TNFα | 34 | 0 | 34 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 17 | 17 | 0 |
| Tryptase | 29 | 17 | 0 | 0 | 0 | 0 | 29 | 29 | 29 | 0 | 29 | 29 | 29 | 0 |
| Histamine | 29 | 29 | 0 | 0 | 0 | 0 | 25 | 29 | 29 | 0 | 29 | 0 | 0 | 12 |

Abbreviations as in Table I.

TABLE VI Clinical laboratory tests performed

| Serum chemistry | Blood hematology | Urinalysis |
|---|---|---|
| Alanine aminotransferase | Hematocrit | Glucose |
| Alkaline phosphatase | Hemoglobin | Bilirubin |
| Aspartate aminotransferase | Red blood count | Urobilinogen |
| Blood urine nitrogen | White blood count | Specific gravity |
| Calcium | Differential count | pH |
| Chloride | Platelet count | Microscopic |
| Direct bilirubin | | Red blood cell |
| Gamma glutamyltransferase | | White blood cell |
| Lactase dehydrogenase | | Bacteria |
| Phosphorus | | Crystals and casts |
| Potassium | | |
| Serum creatinine | | |
| Sodium | | |
| Total bilirubin | | |
| Total protein | | |

TABLE VII Summary of pulmonary function testing in subjects/patients receiving perflenapent emulsion

| Pulmonary function | Baseline | +2 min | +4 min | +6 min | +8 min | +1 h | +96 h |
|---|---|---|---|---|---|---|---|
| Spirometry | 116 | 0 | 25 | 0 | 0 | 116 | 29 |
| Pneumotachometry | 8 | 8 | 0 | 8 | 8 | 0 | 0 |

### Statistical Analysis

Statistical analyses of the comparison of changes from baseline following test article administration were performed. Mean changes from baseline at postdose time points were compared between treatments using paired *t*-test. The number of patients with substantial changes or marked abnormalities from baseline at postdose time points was compared using the Stuart-Maxwell test. Significance for statistical tests was set at the 0.01 alpha level.

### Adverse Events

Adverse events were observed in 743 patients after active control and perflenapent emulsion injections and in 151 patients after placebo injections. An adverse event was defined as any untoward medical occurrence in a patient treated with a test article. The causal relationship of the test article and the adverse event was determined by the physician as not related, possibly related, probably related, definitely related, or unknown. Patients were questioned regarding adverse events with general questions such as "How do you feel?" Only after allowing the patient to volunteer information was more in-depth questioning pursued. The degree of intensity of an adverse event was weighed by the degree of probing required to elicit the response. Patients experiencing adverse events were followed at intervals not exceeding 24 h until an outcome was determined. If the patient was referred to surgery or an additional invasive procedure within 24 h following the study, the patient was questioned regarding adverse effects before the procedure. If an adverse event occurred after the required 24-h follow-up period and came to the attention of the investigator, this adverse event was also reported. The data collected regarding the adverse event were date and time of onset, duration, intensity, treatment, outcome, and the relationship to the test article. The intensity of the adverse event was characterized as "mild," "moderate," or "severe." The investigator's determination of the relationship of the adverse event to study drug was described as "definite," "probable," "possible," "unknown," or "not related."

### Discomfort

Discomfort associated with the injection was evaluated and recorded during administration and within 5 min after administration of placebo and perflenapent emulsion. Patients evaluated the discomfort associated with the injection with regard to type, time of onset, duration, location, and intensity associated with the actual injection. The presence of a particular discomfort was graded by the patient as none, mild, moderate, or severe.

## Results

### Cardiovascular

Mean changes from baseline in blood pressure and pulse rate were generally similar among patients after each test article, and only minor fluctuations were observed at postdose time points. Pre- and postdose values for blood pressure are shown in Figure 1. The majority of patients had similar pre- and postdose blood pressure values, and no changes after perflenapent administration were considered clinically significant by the investigators. The patients represented by filled-in circles in Figure 1 had substantial changes between pre- and postdose values. None of these patients had clinical effects, although one patient who experienced an increase in systolic blood pressure, from 156 to 188 mmHg at 5 min post-

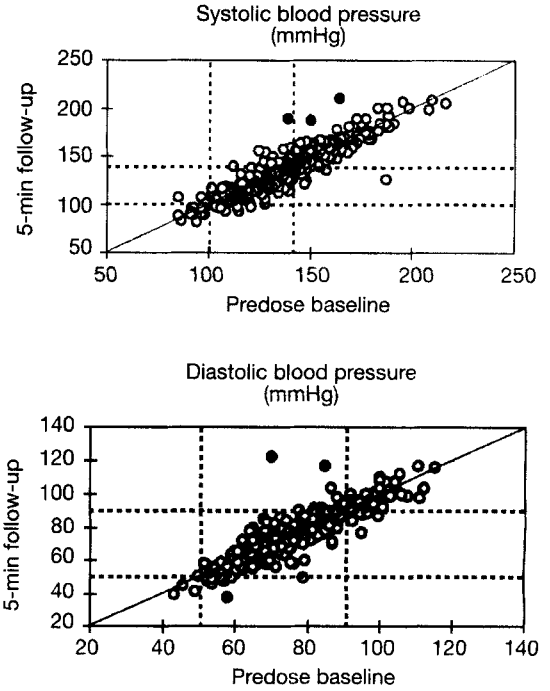


FIG. 1 Systolic and diastolic blood pressure before perflenapent administration and 5 min after administration. Data points with no change between predose and follow-up would be on the diagonal line. Dashed lines indicate the normal range. Filled-in circles are discussed in the text. N = 400.

perflenapent, reported a short (5 s), mild headache that may have been related to the rise in blood pressure. All six patients had values closer to baseline at 30 min and the three patients indicated in the graph of diastolic blood pressure had values within the normal range 30 min after injection.

The only statistically significant ($p \leq 0.008$) difference in mean change from baseline between perflenapent emulsion and active control was seen in the echocardiography studies. Pulse rate at 1, 3, 5, 8, and 12 min postdose showed a greater increase following perflenapent emulsion than the active control. The comparative mean difference in pulse rates for active control versus perflenapent emulsion at these time points were 0.1 versus 1.9 (1 min), 0.1 versus 1.5 (3 min), −0.1 versus 1.5 (5 min), −0.7 versus 1.3 (8 min), and −0.2 versus 1.2 (12 min). These differences were not considered clinically significant. Minor transient, clinically insignificant changes in vital signs are consistent with other contrast agents.

The measured ECG parameters were within the reference range at baseline and following each test article. Mean changes from baseline indicated minor fluctuations, which were similar between the test articles. The difference in mean change from baseline for the Q-T interval between perflenapent emulsion and placebo was statistically significant ($p \leq 0.001$), but was not considered clinically relevant.

Perflenapent emulsion caused no hemodynamic effects or cardiac toxicity as judged by echocardiographic assessment of regional ventricular wall motion analysis and quantitative ejection fraction determination.

Adverse events related to perflenapent emulsion and attributed to the cardiovascular system were hypertension (three, 0.4%) and palpitations (one, 0.1%). These events were mild or moderate and resolved within 10 min.

### Pulmonary

Oxygen saturation remained constant at approximately 95 to 96% throughout the studies regardless of the test article. Minor fluctuations were seen that were not clinically significant. There were no statistically significant differences between treatments at any postdose time point. Respiratory rate (Fig. 2) was generally similar among patients after each test article, and only minor fluctuations were observed at postdose time points. When fluctuations away from normal did occur, as indicated by the filled-in circles in Figure 2, they were not judged clinically significant by the investigator. One patient in this group did experience a headache, but this was judged to be unrelated to administration of perflenapent emulsion. All but 4 of the 18 patients in this group returned to baseline within 30 min.

Pulmonary function tests (spirometry) showed no change from baseline after administration of perflenapent emulsion. Administration of perflenapent emulsion at doses up to 0.10 ml/kg in conjunction with exercise stress had no clinically significant effect on pulmonary function. Measurements of tidal volume by pneumotachometry showed no clinically significant changes following administration of perflenapent emulsion.

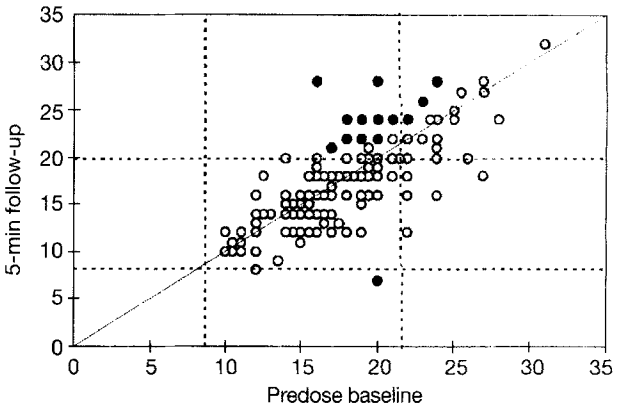


FIG. 2 Respiratory rate (rpm) before perflenapent administration and 5 min after administration. Data points with no change between predose and follow-up would be on the diagonal line. Dashed lines indicate the normal range. Filled-in circles are discussed in the text. N = 394.

Due to the particulate nature of perflenapent emulsion during intravenous administration, it is possible to speculate that patients with significant cardiorespiratory conditions may be at greater risk for adverse events. To assess this possibility, adverse events in patients identified as having significant cardiovascular histories or conditions that may have predisposed them to adverse events following injection of perflenapent emulsion were analyzed. Of the 145 patients assigned to the high-risk group, 17.2% had one or more adverse events compared with 10.5% (78 patients) in the study population as a whole.

### Renal

Serum creatinine (Fig. 3) and blood urea nitrogen (BUN) (Fig. 4) mean values did not change from baseline after administration of perflenapent emulsion. Statistical analysis performed on the measured urine parameters showed no significant effect of perflenapent emulsion at rest or following

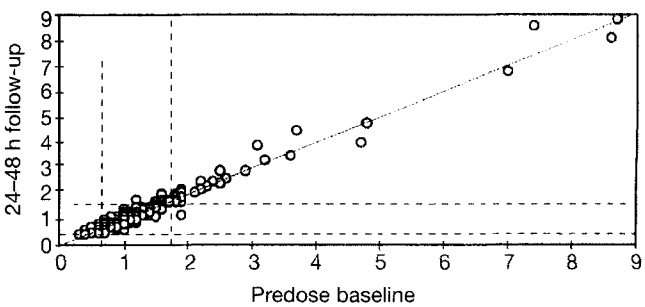


FIG. 3 Serum creatinine (mg/dl) levels before and 24 to 48 h after perflenapent emulsion administration. The dashed lines indicate the normal range. Data points with no change between predose and follow-up would be on the diagonal line. N = 389.

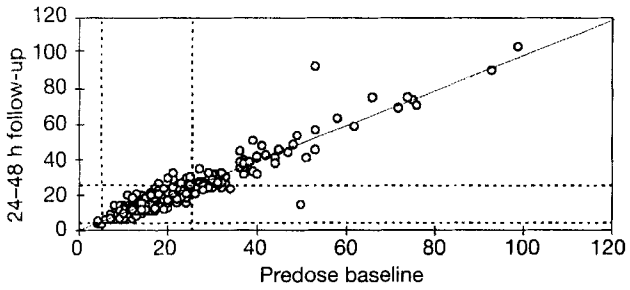


FIG. 4 Blood urea nitrogen (BUN) (mg/dl) levels before and 24 to 48 h after perflenapent emulsion administration. The dashed lines indicate the normal range. Data points with no change between predose and follow-up would be on the diagonal line. N = 381.

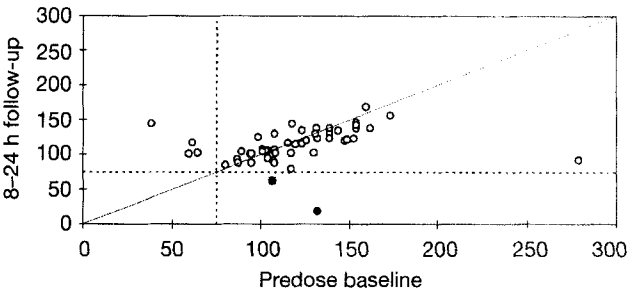


FIG. 5 Creatinine clearance (ml/min) rate before and 8 to 24 h after perflenapent emulsion administration. The normal range is above and to the right of the dashed lines. Data points with no change between predose and follow-up would be on the diagonal line. Filled-in circles are referred to in the text. N = 53.

exercise. Creatinine clearance (Fig. 5) and body surface area-adjusted creatinine clearance showed no dose-dependent or clinically significant effect on renal function after perflenapent emulsion administration. The filled-in circles in Figure 5, which represent values that were within the normal range at baseline and below normal range at 8 to 24 h follow-up, returned to normal range at the 24 to 48 h measurement. These findings indicate that perflenapent emulsion has no clinically significant effect on renal function.

### Immune

Serum was analyzed for histamine and tryptase after administration of perflenapent emulsion to assess complement activation. The statistical analysis performed failed to detect an effect of perflenapent emulsion on histamine, tryptase, or complement activation.

To assess possible vascular endothelial damage, tumor necrosis factor was evaluated in a subset of patients. Administration of perflenapent emulsion did not effect the levels of tumor necrosis factor.

### Hepatic

No significant changes were seen in measures of liver function including total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutamyltransferase (GGT), or lactose dehydrogenase (LDH) following administration of perflenapent emulsion.

### Central Nervous System

Cranial nerve assessments were not affected by perflenapent emulsion. Adverse events related to perflenapent emulsion and attributed to the nervous system occurred in 3.9% (n = 29) of patients. These events consisted of vasodilation (2.8%, n = 21), paresthesia (0.9%, n = 7), dizziness (0.4%, n = 3), and dry mouth (0.3%, n = 2). These events were mild or moderate and resolved within 10 min.

### Hematologic Parameters

Blood was analyzed to test the hematologic and coagulation systems following administration of perflenapent emulsion. The statistical analysis of hematocrit, hemoglobin, red blood count, white blood count, differential counts, and platelet count detected no effect of perflenapent emulsion at rest or following exercise.

### Adverse Events

Table VIII summarizes adverse events by relationship to the test agent and by body system. Fifty patients (6.7%) following perflenapent emulsion and four patients (2.6%) following placebo had adverse events considered related to the test article. The most frequently occurring events (≥ 1%) considered relative to perflenapent emulsion were vasodilation (2.8%) and taste aberration (1.2%).

In general, the adverse events that occurred following perflenapent emulsion were mild to moderate in intensity, started within 10 to 20 min after administration, and resolved spontaneously within 10 to 20 min. Treatment was not discontinued because of adverse events in any patient.

Seven patients (0.9%) experienced moderate adverse events related to perflenapent emulsion. Eight (1.1%) patients had severe adverse events. The adverse events in four of these patients resolved within 20 min without treatment. In the other four patients, these events were considered serious, that is, required hospitalization, and are discussed below.

Seven (0.9%) patients had clinical conditions that resulted in adverse events that were considered serious. One patient had severe fever accompanied by respiratory distress. The fever was considered not related to perflenapent emulsion. The respiratory distress was considered related to the patient's clinical condition and possibly related to the test article because of the temporal relationship to perflenapent emulsion administration. One patient had aortic stenosis resulting in death 7 days after the study; the death was related to the patient's clinical condition and not to the test article. One patient died 9 h after the study; the death was related to the patient's

TABLE VIII Number (%) of patients who experienced adverse events by body system and relationship to test article

| | Placebo (n = 151) | | | Perflenapent emulsion (n = 743) | | |
|---|---|---|---|---|---|---|
| Adverse event | NR | Un | Rel | NR | Un | Rel |
| Any adverse event | 3 (2.0) | 3 (2.0) | 4 (2.6) | 20 (2.7) | 15 (2.0) | 50 (6.7) |
| Body as a whole | 1 (0.7) | 1 (0.7) | 3 (2.0) | 8 (1.1) | 7 (0.9) | 17 (2.3) |
| Cardiovascular | 1 (0.7) | 1 (0.7) | 1 (0.7) | 4 (0.5) | 0 | 4 (0.5) |
| Digestive | 2 (1.3) | 0 | 2 (1.3) | 1 (0.1) | 2 (0.3) | 5 (0.7) |
| Hemic and lymphatic | 0 | 0 | 0 | 1 (0.1) | 1 (0.1) | 0 |
| Metabolic and nutritional | 0 | 0 | 0 | 0 | 1 (0.1) | 0 |
| Musculoskeletal | 1 (0.7) | 0 | 0 | 0 | 1 (0.1) | 0 |
| Nervous | 1 (0.7) | 1 (0.7) | 2 (1.3) | 4 (0.5) | 1 (0.1) | 29 (3.9) |
| Respiratory | 0 | 0 | 1 (0.7) | 3 (0.4) | 3 (0.4) | 5 (0.7) |
| Skin and appendages | 1 (0.7) | 1 (0.7) | 0 | 2 (0.3) | 0 | 9 (1.2) |
| Special senses | 0 | 0 | 0 | 2 (0.3) | 0 | 9 (1.2) |
| Urogenital | 0 | 0 | 0 | 0 | 1 (0.1) | 0 |

*Abbreviations:* NR = not related, Un = unknown, Rel = sum of possibly, probably, and definitely related.

clinical condition. The investigator considered relationship to the study drug unlikely, but because no autopsy was performed and the exact cause of death could not be determined, the adverse event was classified as unknown relationship to the test article. One patient had a headache considered to be possibly related to perflenapent emulsion, clinical state, and study procedure. One patient had severe pericardial perfusion that was related to cardiac surgery and not to perflenapent emulsion. One patient experienced syncope that was unrelated to the administration of perflenapent emulsion. One patient had moderate chest pain considered unrelated to perflenapent emulsion and related to the patient's clinical state.

Given that the patients studied with perflenapent emulsion in these clinical trials had serious concurrent diseases, the observations of these serious disease-related adverse events are not unexpected.

### Discomfort at the Injection Site

The percentage of patients in the controlled clinical studies who had discomfort at the site of injection was 10.6% (16/151) after placebo, 5.7% (23/405) after perflenapent emulsion. The numbers are greater, although not significantly, for placebo. The most frequently reported discomfort for the test agents was coolness at the injection site. Two patients described their discomfort as moderate after perflenapent emulsion and one patient described discomfort as moderate after active control. All other reports of discomfort were described as mild. Most discomfort lasted for ≤ 3 min. Following perflenapent emulsion, the mean onset of discomfort was 6.85 s, and the mean duration was < 1 min.

## Discussion

These studies show perflenapent emulsion to be well tolerated in patients undergoing both echocardiography and ultrasound of other target organs. Perflenapent emulsion is similar in overall tolerability to active control or placebo. No clinically relevant abnormalities in clinical laboratory, pulse oximetry, vital signs, or ECG evaluations were observed, and values following administration of perflenapent emulsion were comparable with those following placebo or active control with respect to changes from baseline. As measured in these studies, perflenapent emulsion had no effect on cardiac, respiratory, renal, or hepatic function. No changes were seen in central nervous system measures.

Adverse events reported are similar to those known to occur with other imaging agents.[7,8] Most adverse events were mild to moderate in intensity, began within 10 to 20 min after administration, and resolved spontaneously within 10 to 20 min.

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