Evaluation of Myelographic Contrast-Medium Tolerance with Psychometric Testing

Clinical tolerance to the myelographic contrast media metrizamide and iopamidol was evaluated in 26 and 30 patients, respectively, with a battery of neuropsychologic tests before and after myelography in a randomized, double-blind prospective study. Twenty hospitalized patients with chronic back pain were also studied before and after computed tomography to serve as controls relative to the groups administered contrast agents. Measures of conceptual reasoning and affect were sensitive tests of adverse reactions. These paralleled the incidence of somatic reactions and correlated with the dose of contrast medium. Methodologic problems included varying intervals between myelography and psychometric evaluation among subjects and use of a less-than-ideal control group. Neuropsychologic tests appear to be sensitive for detection of subtle adverse reactions and possibly predictive of their occurrence. Iopamidol was tolerated better than metrizamide, with somatic side effects occurring in 38% of patients receiving metrizamide and in 17% of patients receiving iopamidol.

Patient tolerance to myelographic contrast media is conventionally evaluated by enumerating the incidence of somatic types of adverse reactions (e.g., headaches, nausea, vomiting, increased back pain), of psychiatric types of adverse reactions (e.g., hallucinations, major mood alterations), and electroencephalographic abnormalities [1-7]. Although valid and useful, these parameters are relatively insensitive to subtle alterations in mentation or affect after intrathecal injection of contrast media and represent poor parameters for evaluating relatively innocuous myelographic media. Such observations have led some investigators to call for more sensitive measures of alterations in mental status [8]. Subclinical disturbances in memory and mood were detected in a large percentage of one group of patients undergoing metrizamide myelography [9].

The purpose of our study was to determine the sensitivity of several neuropsychologic tests for assessing patient tolerance to myelographic contrast media and to compare patient tolerance to two myelographic media, metrizamide and iopamidol, in a randomized, prospective double-blind clinical trial. Psychometric tests were chosen that have been shown to be sensitive to toxic effects of a broad range of psychoactive agents [10]. The tests were of two general types: (1) skill measures and (2) affective/behavioral ratings.

Subjects and Methods

Experimental subjects were 56 patients undergoing myelography and meeting inclusion criteria specified by the Squibb double-blind, prospective study, “Comparison of Iopamidol and Metrizamide Following Intrathecal Administration” (protocol 16272–10, Squibb, Princeton, NJ). After obtaining informed consent, subjects were randomly and blindly selected for metrizamide or iopamidol myelography. A medical control group was also included, comprising 20 hospitalized, chronic-back-pain patients undergoing computed tomography (CT) instead of myelography.

Each myelographic patient was placed on a full liquid diet 8 hr before the myelogram and...
given D5W intravenously throughout the procedure. Patients undergoing cervical myelography via C1–C2 puncture received the 200 mg I/ml concentration. Patients undergoing cervical myelography performed via a lumbar puncture and those having total columnar myelography received the 300 mg I/ml concentration of contrast agent. Thoracic myelography was performed via lumbar injection with the 200 mg I/ml concentration. Patients having posterior fossa cisternography received the 170 mg I/ml concentration. No routine pre- or postmyelographic medications were used.

To keep the radiologist unaware of group assignment, a solution of metrizamide or iopamidol at a predesignated concentration for the specific study was prepared outside the myelographic room and given to the radiologist in a syringe. A 20 gauge needle was used to puncture the subarachnoid space. About 8 ml of cerebrospinal fluid was removed for laboratory analysis. Conventional radiographic and/or CT images were obtained. Patients were kept on a full liquid diet for 8 hr after the procedure.

The characteristics of each group are presented in Table 1. As can be seen, there were no significant differences between the groups in age, education, or gender. The myelographic groups were identical with respect to contrast medium injection sites, type of myelographic study performed, and amount of contrast medium (mg I) used. Although 12 (46%) of the 26 metrizamide patients and 11 (37%) of the 30 iopamidol patients were receiving some form of analgesic, sedative, muscle relaxant, antidepressant medication, or combination thereof on admission to the hospital, the classes of medications represented in each group were comparable. Patients were maintained on their baseline medications throughout the diagnostic procedures.

Myelographic patients were administered a battery of neuropsychologic tests (lasting about 1 hr) before myelography and within 24 hr after myelography. The protocol involved completion of baseline psychometric testing in the morning on the day of the myelogram. The myelograms were obtained in the afternoon, and follow-up testing was done the next morning. For one patient, troubled by nausea and vomiting after metrizamide myelography, testing was postponed until he was well enough to complete the testing (46 hr after myelography).

Most (over 70%) of patients in each myelographic group received follow-up testing 18–24 hr after injection of contrast medium. A few patients (seven receiving metrizamide, five receiving iopamidol) had their myelograms early in the day with follow-up testing scheduled on the same day, usually less than 6 hr after injection of contrast medium. On the average, patients receiving metrizamide were tested 17.7 hr after myelography (SD = 10.6). For patients receiving iopamidol the mean delay was 17.8 hr (SD = 6.8). There was no significant difference between the two myelographic groups in postmyelographic delay of testing (see Table 1). Control patients were tested at a comparable test–reten test interval (mean = 29.5 hr, SD = 21.2). The psychometrician was unaware of the myelographic group assignment.

### Measures

#### Skill Measures

**Memory.** Verbal (free verbal recall test, digit span) and nonverbal (7/24 checkerboard) memory tests were used. These tests have been described in detail [11]. The memory tasks yield six indices: (1) immediate recall of superspan lists/arrays, (2) learning curve with repeated material presentations, (3) proactive interference (difficulties in learning a second set of information after learning a first), (4) retroactive interference (difficulties in recalling the first set after having learned a second), (5) recent memory (recall after a delay of 30 min), and (6) recognition memory.

**Conceptual reasoning.** The Wisconsin card-sorting test [12] was used. The task requires the patient to sort cards into conceptual categories based on performance feedback from the examiner.

**Attention/concentration and psychomotor speed.** Three measures were used in this category: the digit symbol test of the Wechsler variety [13] and the trails A and B test [14] from the Halstead-Reitan neuropsychological battery.

**Fine motor dexterity.** The Lafayette grooved pegboard (Lafayette Instrument Co., Lafayette, IN) was used for both right- and left-hand measures.

#### Affective Measures

**Patient ratings.** The profile of mood states (POMS) [15] was used. The patient rates on a five point scale the extent to which he experiences each of 65 emotion-bearing adjectives. The 65 adjectives are factored into six major affective categories: tension-anxiety, depression, anger-hostility, vigor, fatigue, and confusion. The patient ratings were scored and converted to t scores using the norms of the test publisher. The conversion is made in such a way that higher t scores reflect an increased degree of emotional distress.

**Observer ratings.** The POMS was modified so that the psychometrician rated the patient’s behavior during the testing sessions on the same six affective dimensions of the scale.

Alternate forms of the tests were used on each examination and the forms were counterbalanced in order of presentation for each group. Because of the large number of test variables, group data analyses were first done with multivariate repeated-measure analyses of variance on each skill/affective category. This was followed by inspection of univariate indices of repeated-measure analysis of variance for individual variables. Pairwise comparisons were made where appropriate with analysis of covariance using baseline test performance as the covariate. In addition to psychometric measures, incidences of headaches, nausea, and vomiting, other adverse somatic symptoms, and seizures after myelography were recorded from medical records.

### TABLE 1: Characteristics of Subjects Undergoing Metrizamide and Iopamidol Myelography and of Control Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metrizamide (n = 26)</th>
<th>Iopamidol (n = 30)</th>
<th>Controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Female (p = 0.71)</td>
<td>46</td>
<td>43</td>
<td>55</td>
</tr>
<tr>
<td>Mean age (years) (p = 0.52)</td>
<td>46.3</td>
<td>49.4</td>
<td>45.4</td>
</tr>
<tr>
<td>Mean education (years) (p = 0.99)</td>
<td>13.2</td>
<td>13.1</td>
<td>13.2</td>
</tr>
<tr>
<td>Mean postmyelogram delay in testing (hr) (p = 0.95)</td>
<td>17.7</td>
<td>17.8</td>
<td>§</td>
</tr>
<tr>
<td>Level of injection (no.):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Lumbar</td>
<td>15</td>
<td>19</td>
<td></td>
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<tr>
<td>Study performed (no.):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Total columnar</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cisternography</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mean dose (mg I):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
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<td>1472</td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
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<td>2061</td>
<td></td>
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<tr>
<td>Total columnar</td>
<td>3000</td>
<td>3225</td>
<td></td>
</tr>
<tr>
<td>Cisternography</td>
<td>1000</td>
<td>800</td>
<td></td>
</tr>
</tbody>
</table>

* Chi square.
† Analysis of variance; df = 2.73.
‡ t test; df = 1.54.
§ Interval between baseline and follow-up testing was 29.5 hr.
Results

Skill Measures

Memory. The control and both myelographic groups were found to perform significantly less well on the second testing (univariate trial effects significant of seven of 12 memory indices, \(p < 0.001\)), especially on measures of recent memory. (The finding is thought to represent the effects of proactive interference, i.e., increased difficulty in learning new material after a recent exposure to similar material.) Of the 12 memory indices, only one, a measure of nonverbal learning (checkerboard), showed significant differences between the groups. Metrizamide-injected patients recalled more items after myelography than did iopamidol-injected patients after myelography (\(p < 0.01\)) or control patients on their second testing (\(p < 0.05\)). Iopamidol and control patients performed comparably on follow-up testing, each showing a mild deterioration in performance relative to baseline level. (Multivariate analysis of 12 memory indices yielded group effect, not significant; trial effect, \(p < 0.001\); group X trial interaction, not significant.)

Conceptual reasoning. Since testing of conceptual reasoning was instituted midway through the project, results were available on only a subsample of each group. The results showed a normal practice effect in control and iopamidol-treated patients such that they improved their performance, making fewer errors, on the second testing (fig. 1). On follow-up testing, metrizamide-treated patients made more errors than iopamidol patients (\(p < 0.01\)) or controls (\(p < 0.01\)). While both controls and iopamidol patients had a 40%-50% reduction in errors on the second testing relative to their baseline performance, the metrizamide-treated patients had a mildly deteriorated performance relative to baseline.

(Multivariate analysis was done using three indices of card-sorting performance: total performance errors, perseverative responses, number of categories achieved. The results were: group effect, not significant; trial effect, \(p < 0.001\); group X trial interaction, \(p < 0.05\). Group differences in baseline performance on the three measures were not significant. Univariate trial effects were significant \([p < 0.001]\) for performance errors and perseverative responses, but not for total categories achieved since all groups tended to achieve the maximum number possible. Univariate group X trial interactions on the performance errors was significant \([p < 0.01]\). A similar interaction pattern on the perseverative response measure was found, but was not statistically significant \([p = 0.14]\)).

Attention/concentration and psychomotor speed. No differences were found between groups or consistent trends noted.

Fine motor dexterity. No differences between groups or consistent trends were noted.

Affective Measures

Patient ratings. All three groups reported a reduction in distress on scales of tension, depression, and anger relative to baseline testing (trial effects, \(p < 0.001\); see fig. 2). The iopamidol patients reported a greater reduction in distress than either the metrizamide or control groups (significant only for tension scale, \(p < 0.05\)). All groups reported less vigor (plotted in fig. 2 as increased distress, \(p < 0.001\)). In addition to the tension scale, significant group differences were found on the scales of fatigue (\(p < 0.001\)) and confusion (\(p < 0.002\)). The metrizamide patients reported increased fatigue and confusion after myelography, while the iopamidol patients reported less fatigue and confusion (\(p < 0.01\)). Control patients, generally, reported little change in moods across the scales, as might be expected from a group that has not been confronted by a potentially stressful event. (Multivariate analysis on the six scales yielded: group effect, not significant; trial effect, \(p < 0.001\); group X trial interaction, \(p < 0.05\). There were no significant differences between groups in their pre-myelogram mood ratings.)

Observer ratings. Both myelographic groups were rated as showing increased confusion after myelography relative to the controls; however, only the metrizamide patients were found to be significantly different from the controls (\(p < 0.05\)).

(Multivariate analysis of the six scales yielded: group effect, not significant; trial effect, \(p < 0.001\); group X trial interaction effect, \(p < 0.05\). Significant univariate trial effects occurred
on the tension scale [showing a reduction in distress on the second testing] and scales of vigor, fatigue, and confusion [showing increased distress]. Although multivariate analysis showed a significant group X trial interaction (p < 0.05), univariate indices yielded a significant finding on only the confusion scale.)

Adverse Reactions

Patients having metrizamide myelography had a higher incidence of adverse somatic reactions than did patients receiving iopamidol myelography (table 2). Headaches occurred with nearly equal frequency in metrizamide and iopamidol patients. Nausea or vomiting occurred more often in metrizamide than in iopamidol patients. Seven of the nine patients with nausea and/or vomiting had thoracic or total columnar studies. Only one patient, who had a cervical myelogram with metrizamide, had a seizure after myelography. The seizure occurred about 2 hr after metrizamide injection. The patient was immediately given 130 mg intramuscular phenobarbital, followed by an oral dose the next day. Follow-up neuropsychologic testing of this patient was done 19 hr after metrizamide injection and 3 hr after his most recent dose of phenobarbital. The patient reported a moderate degree of affective distress and showed no improvement in his performance on the conceptual reasoning task over baseline testing.

Several other adverse reactions were noted and were more common in patients receiving metrizamide than iopamidol. These included abdominal, chest, or spinal pain; drowsiness; lethargy; disorientation; and skin rash. Each of these occurred only once and usually in conjunction with either headache, or nausea or vomiting.

Six of the 56 myelographic patients (four metrizamide, two iopamidol) received pharmacologic treatment of their adverse reactions. Three metrizamide and one iopamidol patients were treated for nausea or vomiting. One iopamidol patient was given acetaminophen for headache. The other patient received anticonvulsant therapy for an isolated seizure.

Patients who showed adverse somatic reactions after myelography tended to make more errors in conceptual reasoning (point biserial r = 0.33, n = 23, p = 0.06) and to report more affective distress (r = 0.24, n = 52, p = 0.05). To determine whether somatic reactions, by themselves, were sufficient to account for the postmyelographic group differences in conceptual reasoning and affect, analysis of covariance was performed on postmyelographic test scores. When test variance associated with baseline performance and presence of somatic reactions was statistically removed from postmyelographic test performance, the metrizamide patients continued to show greater difficulty (more errors) in conceptual reasoning (F = 8.23; df = 1.19; p = 0.01) and report more affective distress (F = 10.45; df = 1.48; p = 0.002) than did iopamidol patients.

Dose Effects

Correlations between amount of contrast material used and postmyelographic changes in mood and conceptual reasoning were significant (table 3). Deterioration in mood and conceptual skills was directly related to the amount of contrast material used. The relation was strongest between iodine volume and poor performance (lack of improvement) on the conceptual reasoning task. Patients undergoing thoracic and total columnar studies tended to show more adverse cognitive and affective alterations than those having cervical studies or cisternography.

Discussion

Two shortcomings in this study are worth noting. First, the interval between myelography and testing was somewhat variable and, in most cases, long. This was done as a matter of convenience to the examiner and patients and may not be the optimal interval to detect adverse cognitive and mood alterations. The sensitivity of psychometric testing to adverse reactions may be greater at 6-12 hr after myelography, the time of maximum brain uptake of contrast agent [16]. Routine psychometric evaluation at this time may yield a different pattern of test findings, of differential test sensitivity, than at 18-24 hr. In our study no patients were tested during the 6-12 hr interval and too few were tested before 6 hr after myelography to allow a reasonable comparison of test sensitivity.

Second, the medical control group in our study was included to control for effects of hospitalization, chronic pain, and regimens of analgesic medications. The ideal control

| TABLE 2: Somatic Side Effects after Metrizamide and Iopamidol Myelography |
|-----------------------------------|----------------|----------------|
| Side Effect                        | Metrizamide | Iopamidol |
|                                  | (n = 26)    | (n = 30)    |
| Headache                          | 3 (12)      | 4 (13)      | 0.58  |
| Nausea/vomiting                   | 7 (27)      | 2 (7)       | 0.04  |
| Seizures                          | 1 (4)       | 0           | 0.46  |
| Other†                           | 6 (23)      | 1 (3)       | 0.03  |
| Total‡                           | 10 (38)     | 5 (17)      | 0.06  |

* Fisher exact test.
† Includes abdominal, chest, or spinal pain; drowsiness; lethargy; disorientation, and skin rash.
‡ Number of patients having one or more adverse reactions.

<table>
<thead>
<tr>
<th>TABLE 3: Correlations between Changes in Mood and Card-Sort Performance after Myelography and Dose of Contrast Material Used in Myelography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Contrast dose</td>
</tr>
<tr>
<td>Mood</td>
</tr>
<tr>
<td>Card sort</td>
</tr>
</tbody>
</table>

* Change in total mood-deviation score between pre- and postmyelographic testing.
† Change in total error score between pre- and postmyelographic testing.
‡ p < 0.03.
§ p < 0.002.
subjects would be patients who are also undergoing an anxiety-provoking procedure less invasive than myelography (e.g., spinal tap). Assembling such a group that has no extenuating complications is difficult. Changes in affect cannot be interpreted without suitable controls.

While neuropsychologic measures appear to be sensitive to subtle alterations in mentation, interpretation of psychometric results may not be simple. Some tests are conducive to practice effects with repeated administrations in short intervals of time [17], for example, the conceptual reasoning measures and, to a lesser extent, tests of psychomotor speed and fine motor dexterity used in our study. Others, particularly memory measures with alternate forms, appear prone to produce proactive interference in learning new material (performance deterioration with repeated testing). Until more adequate norms for proactive interference and practice effects are available on specific tests, control patients will likely be needed to assess the contribution of such effects to test performance. Since practice effects are more easily interpreted than interference effects (with interference effects, one is unsure of the cause, e.g., drug or test factors), test selection should favor tasks that minimize proactive interference effects. For example, using the same form of a memory test and computing degree of savings (how much easier did the patient learn the material on the follow-up testing) may be preferred.

An alternative testing methodology for evaluating differential effects of contrast media that eliminates problems of practice and interference effects is one of only doing postmyelographic testing (eliminate the baseline testing). The appropriateness of this methodology hinges on completely randomized assignment of subjects into treatment groups so that baseline group differences are presumably eliminated. If severity of postmyelographic deficit is to be addressed, a control group will need to be included with random assignment. The available statistical procedures for such a methodology are less powerful, however, than in repeated measure designs. Also, information on changes in individual performance after myelography is not available.

In our study, conceptual reasoning and affective measures were sensitive to adverse reactions, while memory, psychomotor speed, and dexterity measures were not. Tests of conceptual reasoning have traditionally been recognized to be among the most sensitive measures of subtle cerebral dysfunction [17]. Conceptual reasoning performance was highly correlated with patient ratings of affective distress, indicating that a systematic evaluation of mood alterations is also useful in evaluating adverse reactions. In general, the disturbances in affect and cognitive functions after myelography were not readily apparent to a trained observer, suggesting that the alterations were relatively mild, subclinical in nature.

Patients undergoing metrizamide myelography showed greater psychometric deficit, reported more affective distress, and had more somatic disturbance than patients receiving iopamidol. A possible exception occurred on one measure of nonverbal memory in which metrizamide patients recalled more items than both iopamidol and control patients. The finding is likely spurious since other nonverbal memory indices did not yield similar findings. However, if one interprets the reduced performance of the iopamidol and control patients as the result of proactive interference, a normal and expected trend, then the metrizamide patients’ failure to show this effect may represent subtle cerebral dysfunction.

It is unlikely that adverse somatic reactions entirely account for the metrizamide patients’ postmyelographic deterioration in conceptual reasoning and affect. When the effects of somatic reactions were statistically removed from postmyelographic test scores, the residual test scores continued to find metrizamide patients to perform more poorly in conceptual reasoning and report more affective distress than did iopamidol patients. Thus, while some decrement in psychometric performance can be associated with somatic distress (i.e., significant correlation), the metrizamide patients’ postmyelographic disturbance in cognition and affect appears in part independent of somatic distress. Similarly, it is unlikely that pharmacologic management of adverse somatic reactions in our study accounts for the group performance differences, since only six patients received any postmyelographic treatment, two of whom had received iopamidol.

Postmyelographic deterioration in cognitive and affective measures was most common in patients having thoracic and total columnar studies. These patients also had higher doses of contrast agent. Whether the functional deterioration was primarily from dose of contrast medium or specific parameters of the procedures (e.g., creating more potential for intracranial migration of contrast media) or a combination of both could not be addressed in our study.

The incidence of adverse somatic reactions in our study, especially in iopamidol-treated patients, was low compared with other reports of metrizamide myelography [5, 6]. In addition to the effect of contrast agents, use of a 20 gauge needle for spinal puncture and routine hydration of patients before and after myelography may have minimized the incidence of such reactions.

In conclusion, select neuropsychologic measures appear to be a valid supplement to other methodologies for evaluating adverse reactions to contrast agents. The results of neuropsychologic testing paralleled the incidence of adverse somatic reactions in our samples and correlated with the amount of contrast agent used and specific types of myelographic procedures. Psychometric measures were also sensitive to differential drug effects. Of the psychometric measures included in our study, conceptual reasoning and affective measures appeared to be sensitive to adverse reactions. Iopamidol was tolerated better than metrizamide.

REFERENCES