Cognitive and Affective Changes After Myelography: A Comparison of Metrizamide and Iohexol

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A battery of brief cognitive tests and a mood scale were administered to 42 patients before and after cervical myelography with either metrizamide (20 patients) or iohexol (22 patients). The patients receiving metrizamide experienced a deterioration in mood after myelography and a relatively greater decline in cognitive test performance than did those receiving iohexol. These two side effects tended to occur together in the metrizamide group, suggesting a common underlying cause; but there was no correlation between changes in mood and cognitive function after myelography with iohexol. These results suggest that metrizamide has a greater neurotoxic effect than iohexol.

It has been known for several years that the use of metrizamide (Amipaque) for myelography can be associated with undesirable side effects, including nausea, headache, back and leg pain, and florid neuropsychiatric symptoms [1–6]. However, the more recent literature suggests that adverse reactions are not limited to spontaneously reported or obviously observable physiological reactions but may include subclinical disturbances of mood and cognitive function that can only be reliably detected by close questioning of the patient and formal psychometric testing [6–10]. Further, there is increasing evidence that the use of other, newer, nonionic contrast media may lead to a reduction in the incidence of these complications [9–14], and an active search for a less toxic alternative to metrizamide has been recommended [15].

Accordingly, we report the results of a study in which alterations in affect and cognitive test performance from a premyelogram baseline were assessed in patients undergoing myelography with either metrizamide or iohexol (Omnipaque), a relatively new nonionic contrast medium.

Subjects and Methods

Subjects were 42 patients in the Presbyterian University Hospital in Pittsburgh who had agreed to participate in another, larger, randomized double-blind trial of the two contrast media for cervical myelography, the results of which have been reported elsewhere [16]. Twenty patients (12 men and 8 women; mean age 43.6 years) were subsequently found to have received metrizamide, and 22 (14 men and 8 women; mean age 49.7 years) to have received iohexol. All patients were tested on two occasions—between 14 and 18 hr before myelography and between 6 and 10 hr after myelography.

Myelograms were accomplished via C1–C2 puncture using 300 mg I/ml concentration for both contrast agents, and all patients were premedicated with 10 mg of Valium. All patients were encouraged to drink liberally before myelography and to consume at least 2 liters of fluid over 8 hr after myelography. Patients were maintained in a head-up position for at least 3 min following myelography, and all received post myelographic CT scans.

Each evaluation took about 1 hr and involved administration of a standard questionnaire about the patient's mood followed by a series of brief cognitive tests. The test battery was designed to be brief yet reasonably comprehensive in terms of the cognitive functions sampled so as to minimize the burden to the patient while maximizing the probability of detecting any

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deficits that might have occurred. It included measures sensitive to verbal and nonverbal memory impairment, disturbances of attention and concentration, perceptual and scanning disorders, constructional apraxia, difficulty with calculation, and some conventional neuropsychological measures of cerebral dysfunction. The group of tests chosen, which should be regarded as a screening battery rather than a full neuropsychological evaluation, yielded a total of 28 scores. The individual tests are described briefly below; a fuller discussion of most of these measures is provided by Lezak [17].

Profile of Mood States (POMS) [18]: A 65-item questionnaire on which the subject rates on a 5-point scale (not at all, a little, moderately, quite a bit, extremely) the extent to which he feels "tense," "miserable," "angry," "lively," "bushed," "muddled," and so on.

Wechsler Memory Scale [17, 19]: A memory scale in standard clinical use that includes measures of general information, orientation, mental control (e.g., counting backward), memory for prose passages, digit span, paired associate word learning, and memory for designs. The visual reproduction subtest was not administered in this study, and since no subject's performance on the information or orientation subtests deteriorated following myelography, they were excluded from the analysis. Different forms were used at the two evaluations to reduce the effect of learning, and 11 scores were derived reflecting immediate and delayed recall of prose and paired associate words, digit span forward and backward, and the three items from the mental control subtest.

Mooney's Visual Closure Test [20, 21]: A measure of visual perception involving recognition of camouflaged faces. The score is the number of correctly identified faces. Even-numbered items were used at the first evaluation and odd-numbered items at the second evaluation.

Repetitive Psychometric Measures [22, 23]: These tests are designed for use in drug studies and involve rapid processing of relatively simple information; subtests include perceptual speed, number facility, visualization, and speed of closure. Parallel forms were used at the two evaluations and, while the subtests used in this study variously demand visual scanning, rapid addition, oculomotor control, and word recognition, all require good concentration. Five scores were derived reflecting the number of items correctly completed within the time limit on each subtest plus the number of errors of addition on the number-facility subtest.

Grooved Peg Board [17]: A manual dexterity test. The two scores are the time taken to insert ridged pegs into 25 keyhole-shaped slots with either hand.

Stroop Color/Word Test [17, 24]: The test involves reading color names, naming colors, and naming the color of the ink in which inappropriately colored color names are printed (e.g., the word "red" printed in green). Scores are the time taken to complete each part of the test.

Trail Making Test [17, 25]: A standard neuropsychological test in which the subject draws lines to connect numbered circles in the appropriate order (part A) or alternates between numerical and alphabetical series (part B). Scores are the time it takes to complete each part.

Rey and Taylor Figures [17]: Parallel forms of a difficult constructional and nonverbal memory task in which the subject must copy a complex geometrical figure and then redraw it from memory after a delay. The scores are the number of elements accurately drawn on each occasion.

Results

Two patients who had been examined prior to myelography declined the postmyelogram evaluation. Two additional patients elected to discontinue the postmyelogram evaluation at an early stage when less than half the tests had been attempted. All four of these patients were subsequently found to have received metrizamide and they were discarded from the analysis. The data reported below, therefore, came from 38 patients, 22 of whom received iohexol and 16 metrizamide.

Changes in expressed mood following myelography as measured by the POMS are shown in Figure 1. Patients receiving metrizamide rated themselves as more anxious, more depressed, more angry, less vigorous, more fatigued, and more confused 6–10 hr after myelography than they had before the investigation. Conversely, patients receiving iohexol reported slightly less anxiety and confusion following myelography (possibly because of relief from worry about the impending investigation) and exhibited virtually no change on

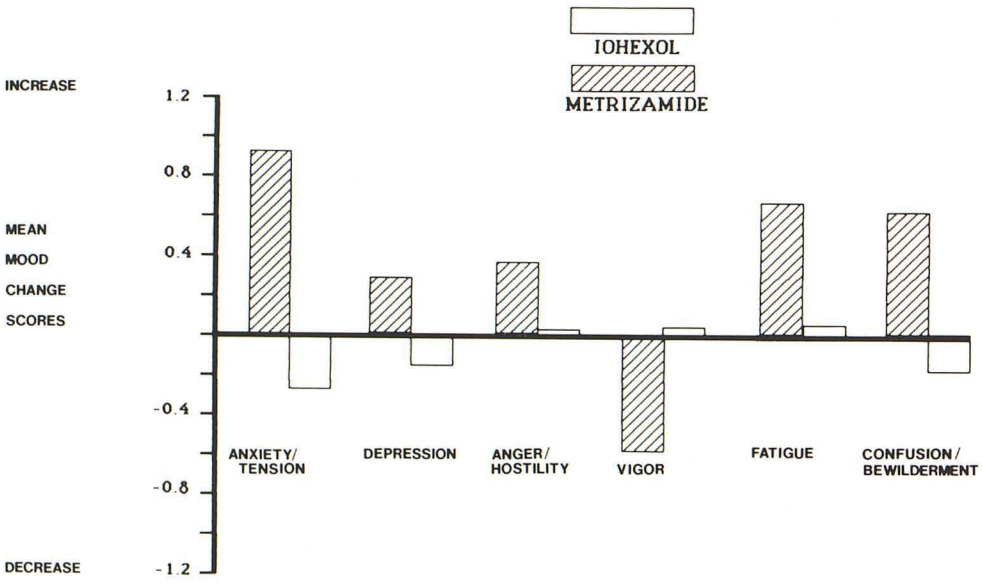

Fig. 1.—Changes in mood following myelography. Mean change from premyelogram baseline on each Profile of Mood States scale is shown for both groups.

the other scales. An overall mood-change score was calculated for each group by subtracting the overall POMS mood-disturbance score obtained at the postmyelogram evaluation from that recorded before myelography. The difference in mood change between the groups was significant at the 0.01 level ($t = 2.99$).

The cognitive test results are not subject to such simple analysis because parallel forms were not available for all the measures used and because the extent of any practice effects attributable to the repetition of the same or similar tests within 24 hr is not known with certainty. Therefore, a simple comparison of pre- and postmyelogram scores on cognitive tests would not necessarily be a valid measure of absolute cognitive change—if normal subjects improved on retesting because of increased familiarity with the task, no change in performance would actually imply a deterioration in level of functioning. However, *relative* change following myelography (i.e., a difference between groups in the *amount* of improvement or decline in test performance from the premyelogram baseline) can be calculated and is a valid basis on which to decide whether one of the contrast media employed has *more* effect on cognitive function than the other. As it is unlikely that the intrathecal injection of either contrast medium would improve cognitive function, it can be assumed that the group that exhibits the greater deterioration after myelography has been more adversely affected by the contrast medium involved.

Bearing this in mind, the difference between pre- and postmyelogram performance was calculated for each subject on each test and the raw difference scores transformed into z scores (i.e., standard deviation units) to allow comparison and summation across tests. An overall cognitive-change score was calculated for each subject by computing the mean of the transformed difference scores for each test. The change scores allow each subject to serve as his or her own control, and the distribution of scores for each group is shown in Figure 2. A t-test applied to the group mean indicates that metrizamide had significantly more adverse effect on cognitive test performance than did iohexol ($t = 3.09$; $p < 0.005$).

Considering the tests individually and excluding the two on which no subject showed any change, the metrizamide group performed less well than the iohexol group on 21 of the 26 measures, a result that departs from chance at the 0.01 level (Fisher exact probability). The between-group difference reached conventional levels of significance on five individual measures (rapid simple addition, immediate recall of a short story, paired associate-word learning, counting by threes and fours, and rapid color naming), all of them favoring the iohexol group.

These two sets of changes, decline in cognitive test performance and deterioration in mood, were correlated in the metrizamide group (rho = 0.489; $p < 0.01$), raising the possibility that a third variable (e.g., fatigue, pain, or nausea) underlies both phenomena. No such relationship was found in the iohexol group (rho = 0.045). Not surprisingly, subjects in either group who spontaneously reported adverse reactions such as nausea, headache, and back pain (five in the iohexol group and 12 in the metrizamide group) tended to experience a deterioration in mood. But there was also a suggestion that

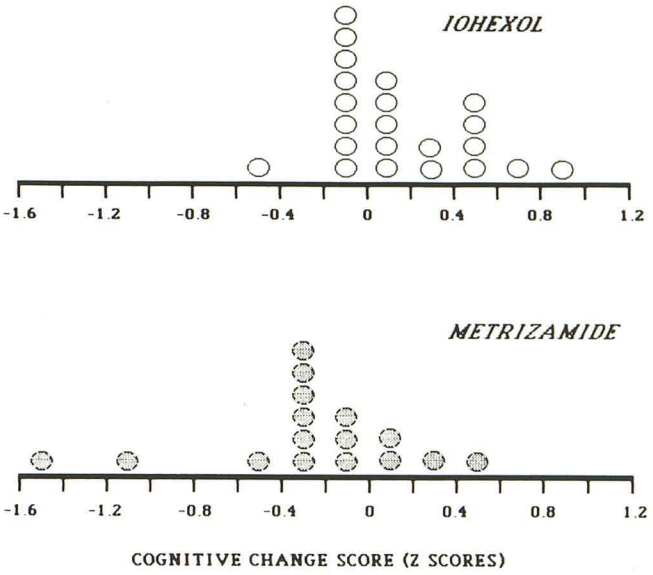

Fig. 2.—Changes in cognitive test performance following myelography. Changes in cognitive test score, averaged across tests and transformed to Z scores, are shown for each subject. Negative numbers indicate relatively poorer performance after myelography.

adverse reactions were associated with greater cognitive impairment in the metrizamide group whereas the cognitive functioning of the few subjects who reported adverse reactions to iohexol did not differ from that of the remainder of the group. Thus, the evidence tends to suggest that such adverse reactions are not by themselves sufficient to account for poor cognitive test performance. However, because of the small numbers and the imbalance in the frequency of adverse reactions between the two groups, no attempt was made to examine this phenomenon statistically, and the conclusion must remain tentative.

Finally, there was no clear relationship between age and either affective or cognitive change following myelography. It is in any case unlikely that our results could be explained on the basis of greater sensitivity of the elderly to the effects of metrizamide [5], as the patients receiving metrizamide in this study were, on average, slightly younger than the iohexol group.

Discussion

Psychometric retesting was performed 6–10 hr after myelography, because it is well known clinically that symptoms are maximal during this period, although they may persist for at least 24 hr [8, 10]. Our results indicate that metrizamide used as a contrast medium in cervical myelography leads to a deterioration in affective state shortly after myelography but that iohexol employed in a similar role does not. Metrizamide also affects cognitive function more than iohexol, but our data do not allow us to conclude with certainty that iohexol has no adverse effects on cognitive test performance.

Although the cognitive test scores of the great majority of

our iohexol subjects remained unchanged or improved after myelography, it is possible that this is attributable to a practice effect—that is, the possibility that subjects who take similar tests twice do better on the second occasion because of their increased familiarity with the material. Further, it is conceivable that unoperated control subjects would have improved to an even greater extent. If this were the case, it would imply that iohexol or the fact of myelography itself had limited the ability of the subjects receiving it to benefit from prior exposure to the test battery. The only way to determine whether the performance of our iohexol subjects was entirely unaffected by the use of this contrast medium would, therefore, be to compare them either with a sham-operated control group or with a group receiving a contrast medium that is *known* to have no adverse effect. The former would clearly be unethical and the latter is not currently possible. Therefore, we conclude only that iohexol has a less adverse effect on cognitive function than does metrizamide, and note that Cronqvist et al. [8] recently reported subtle psychic changes after iohexol myelography though they agree that these are less frequent and much less pronounced than those associated with metrizamide.

Our finding that there was a correlation between the severity of the cognitive deficits and the extent of the deterioration in mood after myelography with metrizamide but not with iohexol, together with the suggestion of a stronger association between these changes and other side effects in the former group, also strengthens the case for a direct neurotoxic effect of metrizamide. It suggests that all these effects have a common cause or may be manifestations of a single underlying disorder, and that the more commonly reported side effects of nausea, headache, back and leg pain, and overt psychic disturbances are only the more obvious manifestations of a more diffuse toxic abnormality.

Galle et al. [9] were able to show that the slowing of mental function 6 hr after metrizamide myelography was directly related to the intracranial concentration of contrast medium at that time but that there was no relationship between mental function and concentration of contrast medium in the subarachnoid space after myelography with iopamidol. Both our results and their findings would be compatible with a direct toxic effect of metrizamide but allow the possibility that some of the milder effects seen after myelography with iopamidol and iohexol are not directly attributable to the contrast medium used. Little or no correlation between mood and level of cognitive function would be expected in patients in whom mood but not cognition had been affected, and postmyelogram changes in mood need not be directly related to myelography. One patient in our iohexol group who became quite depressed after the myelogram had been told that the results, by exclusion, suggested a diagnosis of multiple sclerosis, and it is possible that the diagnosis rather than the myelogram *per se* was the cause of his depression. This may be an extreme case, but anxiety about diagnosis, lack of sleep prior to myelography, and other nonspecific factors can be expected to affect patients' moods.

While the adverse effects of metrizamide myelography reported here are comparatively mild, and there is good reason to suppose that they are transient [9], they are nevertheless definite. The between-group difference in our study accounted for over 20% of the total variance in both cognitive and affective change, and it is possible that this is an underestimate—the four subjects, all from the metrizamide group, who declined to complete the postmyelogram evaluation may well have been more adversely affected by their experience than the remaining subjects; and, had their data been available, the between-group differences may have been greater.

Although the number of subjects included in this study was small, the results suggest that in the absence of any indication to the contrary, and given that the radiographic quality of the two contrast media is equivalent, iohexol may be preferable to metrizamide for cervical myelography because its effects on mental function, if any, are less severe than those of metrizamide.

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