Comparison in myelography between iodixanol 270 and 320 mg/l/ml and iotrolan 300 mg/l/ml: a multicentre, randomised, parallel-group, double-blind, phase III trial

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Abstract The objective of the trial was to compare the safety and efficacy of the non-ionic, dimeric, isotonic contrast medium iodixanol (Visipaque 270 and 320 mg/l/ml) with those of iotrolan (Isovist 300 mg/l/ml) in myelography. After lumbar or cervical puncture, 315 patients were examined in a multicentre, double-blind, randomised, comparative myelography study. Image quality, changes in vital signs, immediate and delayed adverse events were registered. There was a tendency for better images with iodixanol 320 than with iodixanol 270 and iotrolan 300, but the overall quality was good or excellent with all products. The frequency of patients reporting adverse events and headache varied much across centres, but there was no statistically significant difference between the contrast media. The incidence of events was higher after lumbar puncture than after cervical puncture, in women rather than in men, and after puncture with a 22-gauge (G) bevel-tipped needle compared with a 24 G Sprotte needle. The frequency of headache did not correlate with the absence of pathology. The higher iodine concentration in iodixanol 320 could be an advantage for film quality. When compared with iotrolan 300, iodixanol 320 and 270 give similar incidences of adverse events, including headache.

Keywords Myelography · Contrast media · Adverse events · Iodixanol · Iotrolan

Introduction

In spite of more extensive use of magnetic resonance imaging (MRI) for neuroradiological examinations, myelography is still a commonly used technique. Myelography is indeed often superior to MRI in visualising nerve roots and nerve root sleeves, when optimal details are required [1], and in pre-operative assessments when computed tomography (CT) and MRI results are uncertain, especially in combination with CT myelography (myelo CT) [2]. Further, there will still be a need for X-ray myelography in exceptional cases and in hospitals lacking MRI facilities. The intrathecal administration of contrast medium requires radiological products with a high neurological safety. Cases of serious reactions and of neuropsychological disturbance are however still
published, even with the monomeric, non-ionic contrast media and with iotrolan [3, 4, 5]. Iodixanol (Visipaque, Nycomed Imaging AS, Oslo, Norway) is a non-ionic, isotonio [6], dimeric contrast medium, which is well tolerated in cerebral angiography [7, 8] and in other intravascular administrations, with a lower frequency of adverse events such as injection-associated discomfort than the monomeric non-ionic contrast media [9, 10]. The safety of iodixanol in intrathecal administration in adults has been demonstrated in comparison with the monomeric, non-ionic contrast medium, iohexol [11]. Iodixanol preparations differ from the other non-ionic, dimeric contrast medium, iotrolan (Isovist, Schering AG, Berlin, Germany) in electrolyte composition and molecular structure [12]. Iodixanol 320 also has a slightly higher iodine concentration and viscosity than iotrolan 300, which might be important for image quality, especially in thoracic and cervical myelography after lumbar puncture. Improved tolerance to iodixanol compared with iotrolan has been shown in animal studies [13]. In the present study, efficacy and neural safety of iodixanol 270 and 320 mgI/ml are compared with those of iotrolan 300 mgI/ml during myelography in human adults.

**Patients and methods**

The study was approved by the local health authorities and ethics committees, and signed informed consent was obtained from each patient before enrolment in the trial. The trial was performed at three centres: one in Belgium (centre 1 in Genk) and two in Germany (centre 2 in Kassel and centre 3 in Tübingen). Adult patients complying with the pre-established inclusion and exclusion criteria were included during an 8-month period.

A dose of 3.2 gl, i.e. 12 ml of iodixanol 270 mg/ml (IOD270), 10 ml of 320 mgI/ml (IOD320) or 11 ml of iotrolan 300 mg/ml (IOT300), was administered randomly to the patients. The injection site was either cervical (C1–C2), or lumbar (higher L3 or lower L3). Lumbar punctures and injections were performed with a 22-gauge (G) bevel-tipped needle in centres 1 and 3. In centre 2, a 24-G Sprotte needle was used for lumbar puncture and injection, while a 22-G bevel-tipped model was used for cervical puncture and injection. After the examination, all patients were asked to stay in a head-up supine position for 5 h, and in a horizontal position for the next 12 h. All patients were encouraged to drink 2 l more than usual during the first 24 h after the myelography. When medically necessary, a myelo-CT was performed after the myelography without further injection of contrast medium.

Efficacy was evaluated by experienced neuroradiologists assessing the quality of radiographic visualisation in specific areas (e.g. subarachnoid space, nerve roots, vascular formation, etc.) within each main region of the spinal cord; i.e. the thoracic, lumbar and cervical regions. The quality was scored as “excellent” (superior contrast enhancement), “good” (sufficient contrast enhancement to make a diagnosis), “poor” (insufficient contrast enhancement, only limited radiological diagnosis) or “none” (no contrast enhancement). Confirmation of the myelography diagnosis was recorded, when available, either from the myelo-CT or from surgery. For the myelo-CT examination the quality of opacification was rated as “satisfactory” or “not satisfactory”.

Safety was evaluated by recording immediate (up to 24 h after examination) and delayed adverse events (up to 7 days after examination, using a questionnaire), and by recording blood pressure and pulse rate. Adverse events were classified according to the WHO dictionary and serious adverse events were defined and graded according to the ICH guidelines for good clinical practice [14].

The trial was designed as a randomised, double-blind comparative multicentre study comprising a minimum of 100 patients per contrast-medium group. This would provide acceptable 95% confidence intervals for the relative efficacy and safety of IOD270 and IOD320 versus IOT300. The statistical analyses on adverse events consisted of two pair-wise comparisons of the proportions of patients with any adverse event: one comparing IOD270 versus IOT300, the other one comparing IOD320 versus IOT300. Two Fisher’s Exact Tests for 2 × 2 tables were performed for this purpose. Two pair-wise comparisons were performed for the quality of radiographic visualisation, with the combined gradings excellent/good and poor/none. The significance level was set at 5% for all tests. These tests were also done for each centre. There was no correction for multiple testing.

**Results**

Three hundred and fifteen patients were enrolled in the trial, 180 at centre 1, 90 at centre 2 and 45 at centre 3. Three patients were excluded from all the evaluations because the type of contrast medium administered was not known. Safety was evaluated in 312 patients, 192 male and 120 female, with a mean age of 49.2 years (±13.9) and a mean weight of 77.6 kg (±15.6). One hundred and five patients received IOD270, 103 received IOD320 and 104 patients IOT300. Seven more patients were excluded from the efficacy evaluation because a wrong volume (i.e. dose) of contrast medium was given. The three contrast-medium groups were judged to be comparable regarding demographic characteristics (age, weight, gender), concomitant medication, history of allergy, previous surgery, prior reaction to contrast media, presence of risk factors and relevant medical history. A myelo-CT examination was performed in 287 patients. The distribution of the puncture sites, either cervical (C1–C2) or lumbar (higher L3 or lower L3) was comparable in the three contrast-medium groups, with a large majority of lumbar injections (93%). Only centre 2 performed cervical punctures in 12 patients. Intervertebral disc disorder was the most common diagnosis for all three spinal areas, and 8.6% of the patients enrolled had no pathological findings.

**Efficacy evaluation**

Some patients were examined in more than one area of the spinal column, resulting in 54 patients with cervical, 16 with thoracic and 268 with lumbar myelograms (Table 1). After a lumbar puncture, IOD320 provided the highest percentage of excellent quality films for lumbar