

The introduction of myelograms in the early twentieth century heralded an upsurge in severe diffuse adhesive arachnoiditis.

Air was first used for myelography, and then Thorotrast was used, which was highly toxic due to its radioactive nature.

No-one knows how many people were damaged by it, but the numbers were undoubtedly in the thousands.

Oil-based contrast agents such as Myodil (Pantopaque) were introduced after very cursory pre-clinical trials in the early 1940s, despite the animal studies repeatedly demonstrating severe damage to nervous tissue ( [i](#) ; [ii](#) ; [iii](#) );.

They were toxic and caused significant adverse effects as frequently as 74% of cases ( [iv](#) ). These included nerve damage and even demyelination.

An article by Dr. H. L. Feffer, in Medical World News in September, 1978 entitled Arachnoiditis Risk After Myelography, suggested that the at least a quarter of patients undergoing a myelogram (400,000 then being performed every year in the US) develop iophendylate arachnoiditis and furthermore, that those undergoing two or more myelogram studies have a 50% chance of developing iatrogenic arachnoiditis.

Dr. Feffer cited imprecise technique, retention of dye and emulsification of the dye with blood, and stated that animal studies confirm “the devastating effect of iophendylate on the myelin sheath and nerve cells as well as the meninges and nerve roots.”

Over the ensuing 40 years of use, cases of clinically significant adhesive arachnoiditis have also been well documented by many authors ( [\[v\]](#) ; [\[vi\]](#) ; [\[vii\]](#) ).

In 1980, William H. Strain, who was instrumental in developing the clinical use of iophendylate, stated that "millions" of iophendylate myelograms had been performed since its first use in 1942.

He admitted that reactions from the use of his contrast agent were well known, reporting that arachnoiditis may exist in 10-15% of patients who had been investigated with myelography ( [\[viii\]](#) )

In 1962, Mason and Raaf ( [\[ix\]](#) ) reported a case of obliteration of the subarachnoid space by Pantopaque arachnoiditis.

Postmortem findings in the patient, who died seven months after myelography, showed retention of 4ml of dye within the subarachnoid space, complete obliteration of the space with a membrane 1-10mm thick, extensive vacuolisation throughout the outer two-thirds of the spinal cord and parts of the cerebral hemispheres.

The risk of serious adverse effects increases substantially if more than one myelogram is undertaken.

Many authors suggested that it was a combination of the dye and blood in the subarachnoid space (usually during surgery) that caused arachnoiditis, but animal studies showed that the dye alone could be responsible ( [\[x\]](#) ).

Controversy raged for some time over the issue of aspiration of the dye. However, evidence suggested that even with diligent attempts to remove the dye, some residual inevitably remained, causing a toxic reaction ( [\[xi\]](#) ; [\[xii\]](#) ; [\[xiii\]](#) ; [\[xiv\]](#) ).

Bergeron et al. ( [\[xv\]](#) ) noted in their monkey study, that there was always some reaction with retained Pantopaque and that therefore as much dye as possible should be removed after the examination.

Iophendylate persists within the central nervous system, particularly in the basal cisterns and the Lumbosacral region, as either encapsulated droplets (195), which may calcify, or a thin film( [\[xvi\]](#) ; [\[xvii\]](#) ; [\[xviii\]](#) ).

The former can be easily detected on standard X-rays but the latter may be virtually invisible, even on MRI, or misinterpreted as a layer of fat, which it tends to resemble.

It may be that the encapsulated residual dye exerts mass effects locally, or if trauma disrupts the cysts, the dye can escape and cause a chemical inflammation.

The thin film would be more likely to cause a diffuse reaction and possibly a systemic toxic reaction.

Residual dye has been implicated in causing chronic headaches ( [\[xix\]](#) ) and focal seizures ( [\[xx\]](#) [\[1\]](#) ).

Doctors in Sweden were quick to recognise the toxicity of iophendylate and discontinued its use by the 1950s.

However, it was still in use in the UK (as Myodil) and around the world until the late 1980s.

In time, water-soluble agents such as Dimer X and Conray replaced Pantopaque. The early water-soluble dyes were still capable of serious and lasting side-effects ( [\[xxi\]](#) ).

Metrizamide (Amipaque) is particularly linked with risk of seizures and neuropsychiatric disturbance ( [\[xxii\]](#) ).

Later dyes also carried a risk of arachnoiditis, especially if given in too high a concentration or too large a dose.

There have been cases of chemical meningitis caused by water-based myelogram dyes; this may later develop into adhesive arachnoiditis.

Solanki ( [\[xxiii\]](#) ) cites Naylor's 1962 paper suggesting a chemical or autoimmune process may be responsible for neurological damage in arachnoiditis due to contrast media as evidence in favour of a chemical and immunological neuritis.

Iopamidol was introduced in Italy and in Germany in 1981 as the first commercially available non-ionic water-soluble contrast medium approved for myelography. Since then more than 110 million units have been sold worldwide and some 3,000 scientific publications pertaining to its use have been published.

Nevertheless, the **following warning has been issued by the manufacturers:**

1997	
Bracco Diagnostics, Inc. USA and Italy	
IOPAMIDOL	INJECTION, USP
<u>NOT FOR INTRATHECAL USE</u>	
WARNINGS:	
<i>Severe Adverse Events - Inadvertent Intrathecal Administration</i>	
Serious adverse reactions have been reported due to the inadvertent intrathecal administration of	The administration of

Source ( [\[xxiv\]](#) )

In 1997, H.R. 738 was introduced as a Bill in the US House of Representatives, concerning "Myelogram-Related Arachnoiditis Amendments" calling for discontinuance of the use of Pantopaque, Amipaque, Omnipaque and Isovue.

[i] Van Wegenen WP, May 19, 1942, New York Meeting of the Harvey Cushing Society, (Ethyl Iodophenylundecylate) A New Contrast Medium for Visualisation of the Subarachnoid Space

[ii] Jaeger R *Arch. Neurol & Psychiatr.* 1948; 62: 523 Irritating Effect of Iodized Vegetable Oils on the Brain and Spinal Cord

[iii] Hurteau EE, Baird WC, Sinclair E *J Bone Joint Surg.* 1954; 36: 393 Arachnoiditis Following the Use of iodised oil.

[iv] Johnson AJ, Burrows EH *Br J Radiol* 1978 Mar;51(603):196-202 Thecal deformity after lumbar myelography with iophendylate( Myodil) and meglumine iothalamate (Conray 280)

[v] Junck L, Marshall WH *Ann Neurol* 1983 May; 13(5): 469-84 Neurotoxicity of radiological contrast agents.

[vi] Skalte IO *Spine* 1978 Mar; 3(1): 61-4 Adhesive arachnoiditis following lumbar myelography.

[vii] Tabor EN, Batzdorf U *Neurosurgery* 1996 Nov;39(5):1040-2 Thoracic spinal Pantopaque cyst and associated syrinx resulting in progressive spastic paraparesis: case report

[viii] Strain WH. Radiocontrast Agents For Neuroradiology, In Radiocontrast Agents Volume II. 1980, Chapter 9. Page 365-393.

[ix] Mason MS et al. *Journal of Neurosurgery* 1962; 19: 302 Complications of Pantopaque myelography. Case report and review.

[x] Howland, Curry and Butler, *Radiology* 1963 Pantopaque Arachnoiditis: Experimental Study

of blood as a Potentiating Agent.

[xi] Jakobsen *Acta Radiologica (Diagnosis)* 1973; 14(6): 638-646 Clinical evaluation of a histological examination of the side effects of myelographic contrast media.

[xii] Epstein BS, Epstein JA. *Radiology*. 1972 May; 103(2): 353-8. The siphonage technique for removal of Pantopaque following myelography.

[xiii] Keirns M, Wiltse LL. *Clin Orthop*. 1974;0(103): 64-5. Improved technique for injecting and removing pantopaque in myelography

[xiv] Ward W, Matheson M, Gonski A. *Med J Aust*. 1976 Aug 28; 2(9): 333-5. Three cases of granulomatous arachnoiditis after myelography.

[xv] Bergeron RT, Rumbaugh CL, Fang H, Cravioto H. *Radiology*. 1971 Apr; 99(1): 95-101 Experimental Pantopaque arachnoiditis in the monkey.

[xvi] Peterson HO. *Radiology*. 1975 Apr; 115(1): 237-9. The hazards of myelography.

[xvii] Wicke L, Fruhwald F, Neuhold A, Schwaighofer B. *ROFO Fortschr Geb Rontgenstr Nuklearmed* 1987 Dec; 147(6): 663-5

[MR effects of x-ray contrast media]

[xviii] Mamourian AC, Briggs RW. *Radiology* 1986 Feb; 158(2): 457-60 Appearance of Pantopaque on MR images.

[xix] Avrahami E, Cohn DF. *Schweiz Arch Neurol Neurochir Psychiatr*. 1982; 131(2): 157-60. [The problem of postmyelography headaches]

[xx] Greenberg MK, Vance SC. *Lancet*. 1980 Feb 9; 1(8163): 312-3. Focal seizure disorder complicating iodophendylate myelography.

[xxi] Skalpe IO *Radiology* 1976 Dec; 121(3 Pt. 1): 647-51 Adhesive arachnoiditis following lumbar radiculography with water-soluble contrast agents. A clinical report with special reference to metrizamide.

[xxii] Maly P, Bach-Gansmo T, Elmqvist D *AJNR Am J Neuroradiol* 1988 Sep; 9(5): 879-83 Risk of seizures after myelography: comparison of iohexol and metrizamide.

[xxiii] Solanki G *Neurosurgery* 1993; Spinal Arachnoiditis

[xxiv] <http://www.burtonreport.com/InfSpine/DiagnosticMyelography.htm>