

# Thorotrast toxicity: the safety of gadolinium compounds

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In this issue of the Netherlands Journal of Medicine, Kampen *et al.* describe a patient with a hepatic angiosarcoma resulting from exposure to Thorotrast.<sup>1</sup> Thorotrast was developed in 1928 and used as a radiocontrast agent in the period 1930 to 1960.<sup>2</sup> Thorotrast is a colloidal solution containing the naturally occurring radionuclide Thorium. Thorotrast particles are deposited in the reticulo-endothelial cells of the liver, spleen, bone marrow and lymph nodes, retained lifelong, and lead to continuous exposure of surrounding tissue to radiation. It was not until the late 1940s that the first cases of Thorotrast-related malignancies were described, consistent with the long latency interval. In fact, malignancies may occur more than 45 years after drug exposure. Most practising physicians will not be familiar with Thorotrast or only have a vague recollection of this agent from their old study books. As such, the description by Kampen *et al.* may be considered outdated and a case for the historical archives. Still, patients who were exposed to Thorotrast in the 1950s are at increased risk for malignancies, with an estimated cumulative incidence of 35 to 86%!

More importantly, the Thorotrast story points to an important weakness in the procedures that are used for the registration of new drugs, i.e. the detection of unexpected, late occurring, infrequent but severe side effects. Postmarketing surveillance has become more important and is being heavily discussed in the light of recent withdrawals of drugs because of side effects.<sup>3-6</sup> Examples of drugs that have been removed from the market are listed in *table 1*. It is not very surprising that side effects are not recognised in the randomised controlled trials that are used for registration of the drugs. Many studies include no more than 1000 to 4000 patients. In fact, health authorities are satisfied with safety issues if 1500 patients are exposed overall, with 300 treated for at least one year.<sup>3</sup> Side effects that occur in less than one in every 500 patients will not be detected. Furthermore, in the randomised controlled trials patients with comorbidities,

such as renal failure, and patients who use other drugs are often excluded. Side effects may thus occur more frequently in a real-life population but may stay unnoticed for a long time.

In the past year, a new example of an unexpected severe side effect related to a contrast agent has become apparent: gadolinium-induced fibrosing dermatopathy in patients with severe renal failure. International drug authorities such as the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) have recently issued warnings for patients and healthcare professionals.<sup>7,8</sup>

In 2000, Cowper *et al.* described a new skin disorder involving dialysis patients, characterised by thickening of the skin, predominantly involving the limbs.<sup>9</sup> Histologically the skin lesions consisted of irregular bundles of collagen, and an increase in spindled fibroblast-like cells. Shortly thereafter the term nephrogenic fibrosing dermatopathy (NFD) was coined. Several years later it became apparent that in some patients the disorder may progress to a systemic disease (nephrogenic systemic fibrosis, NSF) with involvement of muscle, diaphragm and organs, ultimately leading to death.<sup>10</sup> In 2006, a relationship between NFD/NSF and the use of gadolinium was suggested.<sup>11,12</sup>

**Table 1.** Overview of drugs withdrawn because of safety concerns<sup>6</sup>

Drug	Indication	Side effect
Astemizole	Antihistamine	Cardiac arrhythmias
Cerivastatin	Cholesterol lowering	Rhabdomyolysis
Cisapride	Gastrointestinal motility	Cardiac arrhythmias
Fenfluramine	Obesity	Cardiac valve disease
Nefazodone	Antidepressant	Hepatotoxicity
Terfenadine	Antihistamine	Cardiac arrhythmias
Mibefradil	Hypertension	Drug interactions
Rofecoxib	Antirheumatic	Cardiovascular disease

Grobner described five patients with end-stage renal disease, treated with haemodialysis, who developed NFD within two to four weeks after administration of gadolinium DTPA. Subsequently, 13 cases of NFD were described by Marckman *et al.* All patients had severe renal failure; however, five patients were not yet receiving renal replacement therapy. The first sign of NFD was noted two to 75 days after exposure to gadodiamide. NSF deteriorated and caused severe disability in seven patients, contributing to death in one. Grobner suggested a role for acidosis in the development in NFD; however, this was not confirmed in Marckman's study. A recent case-control study confirmed the association of NFD/NSF with gadolinium exposure.<sup>13</sup> The study contained 19 cases. In a multivariate analysis, exposure to gadolinium was the most independent predictor of the development of NSF. In this study, 18 out of 19 cases had been treated with a gadolinium-containing contrast agent, in four of them the interval between exposure and onset of the disease was more than 12 months. Thus far, more than 200 patients with NFD/NSF have been reported.<sup>14</sup> More than 95% of the evaluated patients were exposed to gadolinium within three months prior to the onset of disease.<sup>14</sup> The incidence of NSF in patients with end-stage renal disease exposed to gadolinium is estimated at 3 to 5%.<sup>14</sup>

Gadolinium is a heavy metal, used as a contrast agent for magnetic resonance imaging.<sup>7</sup> Gadolinium is very toxic, and free gadolinium causes severe hepatic necrosis. Therefore, the currently used gadolinium-containing contrast agents are all chelates, which must ensure that no free gadolinium is present in the circulation. Several chelates are available, and they differ in structure and ionic strength (*table 2*). Still, some free gadolinium will be present and the amount is dependent on the physicochemical properties of the chelate. It has been suggested that the risk of free gadolinium is highest with a linear chelate, and lowest with an ionic, cyclic chelate. Indeed, most reported cases of NFD/NSF have been associated with the use of gadodiamide, and few cases have been described after the use of other linear compounds (*table 2*). The exact mechanism of gadolinium-induced

skin fibrosis is unknown, although it is suggested that gadolinium may cause changes in fibroblast characteristics. It is not surprising that patients with kidney failure are at increased risk, since the half-life of the gadolinium-containing chelate is increased in patients with renal failure. Although limited data are available, it is likely that also the dose of the contrast agent is an important issue.

The health authorities have issued warnings on the use of gadolinium-containing compounds. Kuo *et al.* have recently provided guidelines in a recent review. These authors do not use gadodiamide in patients with a glomerular filtration rate below 30 ml/min. They advise considering alternative imaging techniques in these patients and if magnetic resonance imaging is performed to use the lowest possible dose of another gadolinium chelate. In patients with end-stage renal disease they perform haemodialysis within three hours after gadolinium administration and repeat this after 24 hours. Since haemodialysis results in a better clearance of gadolinium than CAPD, a course of haemodialysis should also be considered in patients undergoing continuous ambulant peritoneal dialysis. If patients are not receiving renal replacement therapy, the benefit of haemodialysis must be balanced against the risk involved with catheter placement, etc. Admittedly, these recommendations are based on expert opinion and not on evidence.

What important lessons can be learned from the Thorotrast and the gadolinium stories? Individual physicians must remain vigilant when using new drugs, and always consider late side effects. It is also important to report suspected side effects. Health authorities must pursue better postmarketing surveillance strategies. With respect to gadolinium, physicians must be aware that severe toxicity can occur, especially in patients with renal failure. Although some compounds may be more toxic than others, we will have to await further studies before we can really consider the cyclic compounds safe. Although NFD/NSF has predominantly been reported in patients with end-stage renal disease, we must keep in mind that toxic effects may occur less frequently, later, and only

**Table 2.** Gadolinium-containing contrast agents<sup>7</sup>

Name	Acronym	Structure	Charge	Cases with NFD
Gadodiamide	Gd-DTPA-BMA	Linear	Non-ionic	Yes
Gadopentetate dimeglumine	Gd-DTPA	Linear	Ionic	Yes
Gadobenate dimeglumine	Gd-BOPTA	Linear	Ionic	No
Gadoxetic acid	Gd-EOB-DTPA	Linear	Ionic	No
Gadofosveset	Gd-DTPA	Linear	Ionic	No
Gadoteridol	Gd-HP-DO <sub>3</sub> A	Cyclic	Non-ionic	No
Gadobutrol	Gd-BT-DO <sub>3</sub> A	Cyclic	Non-ionic	No
Gadoterate meglumine	Gd-DOTA	Cyclic	Ionic	No

after repeated exposure in patients with less severe renal dysfunction. These considerations must be taken into account when considering the best diagnostic strategy in the individual patient.

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