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Gadolinium-containing contrast agents and nephrogenic systemic fibrosis: Long-term consequences of retention in human skin and bone

Nephrogenic Systemic Fibrosis (NSF) is a serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs in patients with severe renal impairment. The disease entity was described in the literature in 2000 (Cowper et al), but it was not until 2006 that a suspected association with the gadolinium-containing contrast agents (GdCAs) was published (Groebner et al). Since then several hundred cases have been identified worldwide and the issue has been kept under close regulatory review.

In December 2007 the Committee for Medicinal Products for Human Use (CHMP) Scientific Advisory Group (SAG) for Diagnostics categorised the GdCAs into three groups of NSF risk based on their thermodynamic and kinetic properties:

High risk:

a) *Linear non-ionic chelates* including gadoversetamide (OptiMARK) and gadodiamide (Omniscan)

b) The *linear ionic chelate* gadopentetate dimeglumine (Magnevist)

Medium risk: *Linear ionic chelates* including gadofosveset trisodium (Vasovist), gadoxetic acid disodium (Primovist) and gadobenate dimeglumine (MultiHance)

Low risk: *Macrocyclic chelates* including gadoterate meglumine (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist)

There is a concern about potential long-term retention of gadolinium in human skin and bone and the consequences in terms of individual risk of developing NSF at a later point in time. This has not been investigated and no studies are planned by the Marketing Authorisation Holders (MAHs) of the above products.

As severe renal impairment is a prerequisite for developing NSF following exposure to GdCAs various theoretical considerations have been put forward, e.g. that a patient who is administered a GdCA at a time with normal renal function, at a later point in time, is at risk of developing NSF, provided that a decrease in renal function takes place for whatever reason.

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A similar theory has been proposed with respect to future changes in bone turnover, e.g. will retained Gd be released, subsequently causing NSF, if an increase in bone turnover occurs for whatever reason in a patient previously exposed to a GdCA.

Data suggest that accumulation of gadolinium in human bone following exposure to GdCAs may be a location for retention of Gd in the body. The CHMP has requested that the MAHs for all GdCAs submit protocols for studies evaluating the potential for long-term accumulation of Gd. Co-factors that may increase the risk of NSF such as serum calcium and phosphate levels at the time of administration of GdCA, and relevant biomarkers should be studied. The testing of bone samples from patients undergoing hip and knee replacement surgery is recommended.

This does not preclude however, the conduct of further studies.