

Linking drugs to obscure illnesses: lessons from pure red cell aplasia, nephrogenic systemic fibrosis, and Reye's syndrome. a report from the Southern Network on Adverse Reactions (SONAR).

Abstract:

Identification of serious adverse drug reactions (sADRS) associated with commonly used drugs can elude detection for years. Reye's syndrome (RS), nephrogenic systemic fibrosis (NSF), and pure red cell aplasia (PRCA) among chronic kidney disease (CKD) patients were recognized in 1951, 2000, and 1998, respectively. Reports associating these syndromes with aspirin, gadodiamide, and epoetin, were published 29, 6, and 4 years later, respectively. We obtained primary information from clinicians who identified causes of these sADRs and reviewed factors contributing to delayed identification of these toxicities. Overall, 3,500 aspirin-associated RS cases in the United States, 1,605 gadolinium-associated NSF cases, and 181 epoetin-associated PRCA cases were reported. Delays in FDA regulation of over-the-counter medications and administration of aspirin to children contributed to development of RS. For NSF, in 1996, the Danish Medicine Agency approved high-dose gadodiamide administration to chronic kidney disease (CKD) patients undergoing MR scans. Overall, 88 % of Danish NSF cases were from two hospitals and 97 % of United States' NSF cases were from 60 hospitals. These hospitals frequently administered high-doses of gadodiamide to CKD patients. Another factor was the decision to administer linear chelated contrast agents versus lower risk macrocyclic chelated agents. For PRCA, increased use of subcutaneous epoetin formulations to CKD patients, in part due to convenience and cost-savings considerations, and a European regulatory requirement requiring removal of albumin as a stabilizer, led to toxicity. Overall, 81, 13, and 17 years elapsed between drug introduction into practice and identification of a causal relationship for aspirin, erythropoietin, and gadodiamide, respectively. A substantial decline in new cases of these sADRs occurred within two years of identification of the offending drug. Clinicians should be vigilant for sADRs, even for frequently-prescribed pharmaceuticals, particularly in settings where formulation or regulatory changes have occurred, or when over-the-counter, off-label, or pediatric use is common.