REVIEWS

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)

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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.

KEY WORDS: pure red cell aplasia; nephrogenic systemic fibrosis; Reye's syndrome.
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INTRODUCTION

Serious adverse reactions (sADRs) caused by commonly used drugs can elude detection for years.[1] Post-marketing changes in practice, target populations, formulation, and dosing can lead to sADRs. Reye's syndrome (RS), nephrogenic systemic fibrosis (NSF), and pure red cell aplasia (PRCA) are three sADRs that were clinical mysteries when first identified in 1951, 2000, and 1998.[2–4] Unexpected associations with pharmaceuticals were published 29, 6, and 4 years later, respectively.[4–7] Overall, 81, 13, and 17 years elapsed between introduction of the implicated drug into practice and identification of the causal relationships with these three unique sADRs. Responses of clinicians, consumers, regulators, and man-

ufacturers led to large decreases in new cases and eventual virtual eradication. In this manuscript, we collaborated with investigators who identified causal relationships between these three pharmaceuticals and their related sADRs and evaluated factors contributing to delays in identifying the causal relationships as well as contributing to virtual eradication of the toxicity shortly after causal relationships were identified.

CASE STUDY METHODOLOGY

Study co-authors identified sADRs characterized by: associated clinical syndromes were not originally listed in product labels; implicated pharmaceuticals had been administered to >10 million individuals; following sADR characterization, reports of new cases of the individual sADRs decreased; and the implicated pharmaceuticals are still marketed. We then invited the investigators who identified causal relationships to participate in the case-study evaluations: RS (KMS) , NSF (HST), and PRCA (CLB, DC). Information was provided on clinical findings, epidemiology, and eradication. Publications (MeSH keywords—NSF, RS, and PRCA) and regulatory notifications (1980–2010) were reviewed for information on epidemiologic and causal investigations, and risk-minimization interventions.

RESULTS

Reye's Syndrome

Aspirin has been marketed worldwide since 1899. Of note, the 1938 Food and Drug Act requiring safety evaluations of *new* drugs did not apply to salicylates as it was not a new drug. It was not until 1962 when the FDA received regulatory authority for all over-the-counter drugs that a long process of evaluation of aspirin safety was begun.

Early reports in the 1910s had noted individual variation in aspirin dosages producing toxicity.[8] Pediatricians in the first two decades of the 20th century frowned upon aspirin's use for fever.[9,10] However, by 1930, children's dose recommendations appeared in textbooks. Despite reports showing salicylate accumulation in some children, marketing of "children's aspirin" began in the late 1940s.[11] Advertisements described aspirin as "gentle" although large numbers of aspirin-associated deaths due to accidents and presumed overdosing in children occurred.[12–14]

In the 1920s, case reports described encephalopathy with liver pathology among children with various illnesses.[15] In 1963, Reye et al. reported clinical and pathology findings for "Reye's Syndrome" cases at one Australian hospital.[3] Encephalopathy occurred in 21 children, including 17 deaths, since 1951. Onset generally began within days of mild illnesses, and was characterized by vomiting, irritability, agitation, stupor, or coma with hyperpnea, decreased cerebrospinal fluid glucose, elevated alanine aminotransferase and aspartate aminotransferase levels, and cerebral edema. Reye also identified a rarely reported pathology finding, hepatic microvesicular fatty degeneration that was later detailed by Partin et al.[16] Some investigators implicated aspirin.[17,18] Others countered that RS patients had low, presumably non-toxic, salicylate levels despite observations that salicylate levels decrease rapidly and correlations between salicylate levels and toxicity are poor.[19,20]

Regulatory and manufacturer considerations loom large in explaining why there was a significant delay in the identification of the cause of RS. (Table 1) The FDA had little authority for over-the-counter medications until 1962. Although a preliminary FDA panel report on aspirin published in 1977 expressed concern with advertisements and salicylate accumulation and recommended children

Table 1. Perfect Storms of Regulatory, Practice, Product, and Technology Changes Resulting in Development of Novel Serious Adverse Drug Reactions Years After the Implicated Drug Was Introduced

Agent (1st regulatory approval date)	Gadolinium (1989)	Erythropoietin (1989)	Aspirin (approx. 1899)
Toxicity (date that syndrome was first identified)	Nephrogenic systemic fibrosis (2000)	Pure red cell aplasia (1998)	Reye's syndrome (1951)
# of patients in initial report identifying the probable cause of the sADR (year)	5 and 13 (two independent reports) (2006)	12 (2002)	7 (1980)
Regulatory	Danish approval of triple-dosing of GBCAs to CKD patients	Requirement to reformulate Eprex with polysorbate 80	Salicylates "grandfathered" by 1938 Drug Safety Act and "studied" by FDA committee after 1962 Kefauver Amendment
Practice	Change from CT to MR scanning; off-label use of triple-dosing of GBCAs in the United States	Subcutaneous administration	Pediatricians and parents administered aspirin to children with fevers and childhood illnesses
Product	Linear versus macrocyclic chelation of GBCAs	Eprex with polysorbate 80 vs. other erythropoietins	Not applicable
Techno-logy	MR scanners improved to handle triple-dosed GBCAs	Recombinant technology allows for erythropoietin development	Not applicable
Rate	3 % to 18 % reported at certain hospitals[41]	5 per 100,000 Eprex treated individuals[7,51]	Up to 5.6 cases per 100,000 <17 years of age[62]

with fever not receive aspirin for more than 3 days without consulting physicians, no requirements regarding product labels had been issued.[21] Identifying the probable cause of RS remained elusive until 1980.[6] In 1978, a resident physician informed a Centers for Disease Control (CDC) epidemiology officer at the Arizona Department of Health Services that seven children developed Reye's syndrome during a local influenza A outbreak. In 1980, the CDC officer and her collaborators reported that among these children and 16 ill classmate controls, case patients were more likely to be febrile and to have received salicylate-containing medications and higher salicylate doses.[6,22] Reports of studies in Ohio and Michigan also implicated salicylate.[23–25] In 1983, Starko and Mullick reported hepatic microvesicular fat patterns in children with therapeutic salicylate intoxication, findings previously reported with RS.[26] In 1988, clinical risks were reported with increasing daily aspirin doses at all levels below "recommended" (65–80 mg/kg/day) doses and were also associated with dosing on days three and four.[27]

Efforts to raise awareness of the link between aspirin and RS included journal publications; warning statements in 1982 by CDC consultants, the American Academy of Pediatrics, and the United States' Surgeon General; and a "Black Box" warning in 1986 advising against administering aspirin to children and teenagers with chicken pox or flu symptoms without consulting a physician.[6,24,25,27–33] The British Risk Factor Study found excess aspirin exposure in RS children and a 1986 advisory by the Committee on Safety of Medicines warned against administering aspirin to children under twelve.[34] Warning labeling on aspirin containing preparations was introduced, and modified in 2003 to warn against giving aspirin to children under sixteen without consulting a physician. In the United States, 555 cases of RS were reported in 1980. Following publication of the link between aspirin and RS, use of aspirin among infants, children, and teenagers decreased.[35] Fewer than 37 cases were reported annually from 1987 to 93, and fewer than two cases were reported annually from 1994 to 1997.[36] RS incidence declined in England beginning in the mid-1980s.[34] At least thirteen countries have issued RS warnings.[34]

Nephrogenic Systemic Fibrosis

Beginning in 1993, the gadolinium-based contrast agent (GBCA), gadodiamide, received regulatory approvals for contrast enhancement of Magnetic Resonance Imaging (MRI) scans.[37] Approvals were subsequently received in 90 countries (0.1 mmol/kg dosing).[37] In 1996, gadodiamide received FDA approval for 0.3 mmol/kg dosing for brain MR imaging and Danish regulatory approval for general MR imaging. In 1998, Danish contra-indications for gadodiamide administration to CKD patients were revoked in 1998.[37,47,48]

Gadodiamide use rapidly expanded in the late 1990s due to favorable comparisons versus iodine-containing contrast media and its regulatory approval in several countries for use at higher doses (0.3 mmol/kg dosing) for brain and/or general MRI scans. Worldwide, 40 million gadodiamide doses have been administered since 1993.[37,38]

In 2000, Cowper et al. reported a new syndrome, nephrogenic fibrosing dermopathy (NFD), characterized by severe progressive skin, joint, and muscle deformities.[2] Fourteen NFD patients had received or were undergoing hemodialysis. By 2003, systemic involvement was identified, and the syndrome was renamed NSF.[39] Early disease was characterized by narrow collagen bundles in the skin, with abundant edema fluid and mucin separating the lesions. Fibrocytes, distributed between collagen strands with elastic fibers, were immunohistochemically CD34 positive.

In 2006, clinicians from Herlev Hospital in Denmark reported to the Danish Medicines Agency (DMA) that 13 chronic kidney disease (CKD) patients developed biopsy-confirmed NSF.[5] Patients had received gadodiamide enhanced MRIs. Lifetime gadodiamide doses in adult patients with disabling NSF were greater than in patients with non-disabling NSF or in controls.[40] NSF patients had mean 25-day symptom-free periods following gadodiamide administration.[40–42] Three months earlier, an Austrian nephrologist reported that five of nine CKD patients who had undergone gadodiamide-enhanced MRIs developed NSF.[43] In 2008, Marckmann reported that between 2001 and 2006, 18 % of CKD patients at Herlev Hospital with severe renal insufficiency had developed NSF following administration of high-doses of gadodiamide.[41]

Several factors account for NSF development. (Table 1) The type of chelation of gadolinium in GBCAs is important. Basic science studies identifying an unstable linkage between the linear chelate and gadolinium in the gadodiamide formulation was reported to the manufacturer of gadodiamide in 1995 (although this report was only publicly released by the Danish Medicines Agency in March 2012).[44] The European Medicines Agency (EMA) and the FDA initially disagreed on product specific rates of GBCA-associated NSF, with the EMA categorizing linear-chelated GBCAs as high-risk for NSF and the FDA, prior to 2010, categorizing the toxicity as occurring with linear- and macrocyclic chelated GBCAs.[38] Since 2010, the EMA and FDA have both characterized non-ionic linear-chelated GBCAs as high NSF-risk, and macrocyclic GBCAs as low-risk.[44,45] Overall, 70 % of cases are associated with gadodiamide and 20 % with gadopentetate dimeglumine, both are linear chelated GBCAs.[38] NSF cases occur among patients with CKD or estimated glomerular filtration rates <30 mL/min/1.73 m^2.[46] An additional risk-factor was high erythropoietin dosages, a practice that was more common in the United States versus other countries.

FDA databases include 1,603 NSF reports, 93 % from the United States (US) and 4 % from Denmark.[38,47] The first reports were in 1997 and the peak number of reports occurred in 2005. Overall, 60 hospitals accounted for 97 % of the 1,493 United States cases and two Danish hospitals accounted for 88 % of the 66 Danish NSF cases described in the FDA Adverse Event Reports database.[38,47,49] Beginning in 1996, the 60 US hospitals with the majority of the NSF patients, primarily centers with large renal transplant programs, began performing body MRIs on large numbers of CKD patients with off-label high doses of gadodiamide (0.3 mmol/kg).[38] In Denmark, in 1997, clinicians at one large Danish Hospital, Skejby Hospital, began administering triple-dose gadodiamide to CKD patients for body MRIs – a setting that had received approval in several European countries, including Denmark (beginning in 1996). The first Danish NSF cases developed at Skejby Hospital in 1997, although these cases went unrecognized until 2009.[47,49] A second Danish hospital, Herlev Hospital in Copenhagen, had purchased an MR scanner in 2001 suitable for GBCA use and beginning in 2002, had adopted the practice of administering high gadodiamide doses to CKD patients seeking to identify optimal renal transplantation candidates. In contrast, relatively few CKD patients had received triple-dose gadodiamide at the 36 Danish hospitals where 12 % of the Danish NSF cases were identified and in the 2,040 other US hospitals where 3 % of the United States' NSF cases were identified.[38] In many European countries other than Denmark, gadodiamide had received regulatory approval for 0.3 mmol/kg dosing, although it is not known if high doses were administered. Some Eurocentric European countries preferentially administered lower risk macrocyclic chelated GBCAs as these products were manufactured in Europe. The combination of low rates of use of high doses of gadolinium-based contrast agents and preferential administration of low-NSF risk gadolinium-based contrast agents in most European countries may account for low numbers of reported cases of NSF from these countries.

In Denmark, after the first NSF cases were reported to the DMA in 2006, no new NSF cases developed at the two Danish hospitals where 88 % of the Danish NSF cases had developed.[47] Radiologists at Herlev Hospital immediately and voluntarily discontinued administering gadodiamide in 2006 after reporting a probable causal relationship between gadodiamide and NSF. Radiologists at Skejby Hospital subsequently discontinued administering gadodiamide to CKD patients after being informed of the practice change adopted by radiologists at Herlev Hospital.[47] In 2007, Danish and European regulatory agencies contra-indicated use of three linear-chelated GBCAs in patients with severely reduced renal function and advised caution when administering these agents to persons with moderately reduced renal function.[44,47] In the United States in 2006, many radiologists voluntarily discontinued administering all GBCAs to CKD patients after the FDA reported that 25 cases of GBCA-associated NSF had been reported in Denmark and Austria in 2006 and NSF reports subsequently and rapidly declined.[38] In 2009, manufacturers finally issued "Black Box" warnings against administering GBCAs to CKD patients, GBCA use diminished further, and no new NSF cases have been reported since then.[38] In 2010, FDA required the manufacturers of the three high-NSF risk linear chelated GBCAs to add Black Box warnings against administering these agents to persons with acute kidney injury or CKD, while similar warnings are not included in product labels for the other FDA-approved GBCAs.[46]

Pure Red Cell Aplasia

Beginning in 1989, recombinant erythropoietin received regulatory approvals internationally for anemia prevention. In 1998, because of concerns that albumin stabilizers could transmit variant Creutzfeldt-Jakob disease, the European Medicines Agency required erythropoietin to be reformulated with polysorbate-80. Tens of millions of patients outside of the United States received this formulation. In that same year, the FDA subsequently received reports of three CKD patients in France who developed PRCA.

Four years later, Casadevall et al. described PRCA requiring frequent red blood cell transfusions developing in 13 CKD patients.[4] Twelve had been treated with epoetin alfa and one with epoetin beta and PRCA developed after 3 to 67 months of treatment. Serum from PRCA patients blocked formation of erythroid colonies by normal bone marrow cells. Inhibition was reversed by epoetin.

In 2004, Bennett et al. reported 181 CKD patients who developed epoetin-associated PRCA at a median of nine months of epoetin treatment.[7] Most patients were male, undergoing hemodialysis, and all had CKD. All had received epoetin subcutaneously; 95 % received the epoetin-alfa formulation with polysorbate 80. Most were from regions where epoetin was administered subcutaneously to CKD patients. Independently, Cournoyer et al. reported subcutaneous administration of epoetin alfa with polysorbate 80 had the highest PRCA incidence rates.[50] In 2005, the groups collaboratively reported that epoetin-associated PRCA disappeared following renal transplantation.[51] In 2009, epoetin-associated PRCA resolved in 13 of 14 patients who received a novel peptide-based erythropoietin-receptor agonist.[52]

PRCA from increased use of subcutaneous epoetin was facilitated by several factors (Table 1). In the mid-1990s, a shift from intravenous to subcutaneous epoetin administration to CKD patients occurred as trials reported clinical effectiveness and cost-savings. In 1998, reformulated epoetin-alfa with polysorbate 80 stabilizer began to be

marketed outside of the United States. Epoetin-associated PRCA cases were reported from countries where epoetin alfa with polysorbate-80 was administered subcutaneously to CKD patients. Epidemiologic, chemical, and immunologic data supported the hypothesis that leachates from uncoated rubber syringe stoppers caused increased PRCA incidence associated with epoetin alfa with polysorbate 80.[53] Exposure-adjusted PRCA incidence rates with subcutaneous administration of this formulation increased in France, England, and Spain between 1998 and 2001 and in Canada until 2002 to 18 cases per 100,000 epoetin alfa with polysorbate 80 treated CKD patients.[7,50] After regulatory advisories warned against disrupting cold chain storage conditions or administering epoetin alfa with polysorbate 80 subcutaneously, and Teflon-coated rubber stoppers were added to prefilled epoetin alfa syringes, PRCA incidence subsequently decreased by 90 % in France, the United Kingdom, and Spain and by 80 % in Canada.[7,53]

DISCUSSION

Astute clinicians first identified RS, PRCA, and NSF syndromes. Causal relationships were not widely accepted until epidemiologic studies implicating aspirin, erythropoietin, and gadodiamide with these syndromes were published.[5–7] These reports appeared 81, 13, and 17 years, respectively, after the implicated drugs had been introduced into practice.

A confluence of factors explains development of these sADRs. Regulatory considerations include removal of renal contra-indications and approval of high-dose administration for gadodiamide in Denmark, minimal oversight of over-the-counter medications for salicylates, and epoetin reformulation in Europe. Another factor is off-label administration of triple-doses of gadodiamide to CKD patients in the United States. Other contributors included clinician decisions, such as choosing to administer epoetin subcutaneously and administering high doses of gadodiamide to CKD patients in an effort to improve visualization. Clinical settings such as CKD and pediatrics are also important. Immunology played a role, as subcutaneous, but not intravenous, administration of epoetin resulted in antibody formation. These "perfect storms," representing confluences of factors, resulted in sADR development.[6,37,54,55]

Vigilance for these safety concerns is also important.[56] Recently, two cases of neutralizing antibodies were reported during a pre-marketing clinical trial of a biosimilar epoetin (HX575). The product was subcutaneously administered to CKD patients, Detailed analyses found that contamination by tsungsten during the manufacturing of the syringes used for the primary packaging was the most likely cause of protein denaturation and aggregation, which may have led to the occurrence of toxicity in these two patients.[57,58]

After the relationships with the drugs were reported, voluntary changes by physicians in prescribing gadodiamide and epoetin alfa and by physicians and parents in changing aspirin use in children resulted in declines in PRCA/NSF and RS reports, respectively. Publication was important, given that several groups were investigating causal relationships at the same time. For NSF, reports of a gadodiamide-NSF relationship from Austria and Denmark were published three months apart and for PRCA, reports from the United States/Europe and Canada were published on the same day.[5,43,50,51] For RS, a preliminary report of the Arizona case–control study in the *Morbidity and Mortality Weekly Report* in July 1980 was followed by preliminary and final reports of Michigan and Ohio studies with similar findings six and 18 months later, respectively.[22–25] Regulatory responses were delayed and uncoordinated. Canadian notifications of contra-indications for epoetin and PRCA were disseminated one year after European dissemination.[55] In the United States, "Black Box" warnings for gadodiamide and aspirin appeared four and five years, respectively, after roles of these drugs were identified.[45] Delays in toxicity disappearance mirrored regulatory delays. The virtual disappearance of RS occurred after the warning label was required in 1986.[59] Edward Mortimer, a Reye's researcher wrote, " There are many frustrating examples of public health programs that have been thwarted, delayed, or weakened by political pressures from such [special interest] groups. The successful use of less than absolute proof of causation as a shield to protect special interests is epitomized by the sad saga of aspirin and Reye syndrome. A group of aspirin manufacturers and their attorneys exploited the recognized but, on balance, inconsequential epidemiologic problems in the studies that linked Reye syndrome to aspirin…"[60] The potential for manufacturers to delay regulatory notifications should be addressed.[61]

sADRs should be anticipated particularly when pharmaceuticals are administered in settings where formulation or regulatory changes have occurred, or over-the-counter, off-label, or pediatric use is common. Traditional safety efforts that depend on voluntary sADR reporting are unlikely to identify many important toxicities until large numbers of individuals are treated with the implicated drug. Absent active surveillance, our review reinforces central roles of clinicians in suspecting toxicity occurrences, particularly when faced with clusters of patients who have experienced unusual clinical events, and collaborations among clinicians, scientists, public health agencies, and industry in eradicating sADRs.

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