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A Review on Arthroprosthetic Cobaltism: Manufacturer's Product liability for causing Iatrogenic Cobalt toxicity

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ABSTRACT

Cobalt toxicity is a well-documented complication of total hip arthroplasty (THA) when cobalt-chrome implants are utilized. A recent area of attention is "cobaltism," which results from cobalt exposure from cobalt-containing orthopedic implants, chemistry kits, weather indicators, antiquated anemia therapies, cement, fly ash, dyes, mineral wool, asbestos, molds for ceramic tiles, mining, porcelain paint, orthopedic implants, and dental hardware. Like other transition metals, cobalt is a multiorgan toxin. Organ systems affected by acute cobalt poisoning include endocrine, gastrointestinal, central and peripheral nervous system, hematologic, cardiovascular, and metabolic. Chronic inhalational exposures affect the pulmonary system and dermatologic system.

INTRODUCTION

Like other metals, cobalt occurs in elemental, inorganic, and organic forms. Organic cobalt exposure results from cyanocobalamin (vitamin B12) ingestion, but due to its limited oral absorption and its rapid renal elimination it is considered of low toxicity. Elemental cobalt (Co) toxicity is reported through both inhalational and oral exposures. Medicinally, cobalt chloride was combined with iron salts and marketed in the 1950s as "Roncovite"—for the treatment of anemia due to its ability to stimulate erythropoiesis. As recently as 1976, physicians still used cobalt salts to reduce transfusion requirements in anemic patients, despite well-known adverse effects. Inorganic cobalt salts, such as cobaltous chloride (CoCl2) and cobaltous sulfate (CoSO4), were historically used for the treatment of anemias. The other common medical use of cobalt is as a radioactive isotope, cobalt-60 (60Co). This γ emitter was formerly used in the radiotherapy of cancers but has been largely replaced by linear accelerators in the Western world. Radioactive Cobalt used for radiation therapy is associated with radiation burns. Epidemics of cardiomyopathy and goiter termed "beer drinker's cardiomyopathy" and "cobalt-induced goiter" occurred between the 1960s and the 1970s. During this period, cobalt sulfate was added to beer as a foam stabilizer. In the 1970s, these epidemics were halted with the discontinued use of cobalt sulfate for this purely esthetic purpose. The most significant source, however, arises through the formation of cemented tungsten carbide, a "hard metal." In tungsten carbide factories, powdered cobalt and tungsten are combined through an intense sintering process that exposes the metals to hydrogen that has been heated to 1832°F (1000°C). The

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first published investigation of these factories reported a 10-fold increase in workspace cobalt concentrations compared to atmospheric concentrations. These respiratory exposures result in pulmonary toxicity, known as "hard metal disease." Like other transition metals, cobalt is a multiorgan toxin. Co2+ inhibits several key enzyme systems and interferes with the initiation of protein synthesis.

DISCUSSION

Cobalt toxicity is a well-documented complication of total hip arthroplasty (THA) when cobalt-chrome implants are utilized. Although it is most commonly associated with metal-on-metal bearing surfaces, there are multiple reports of cobalt toxicity following revision of a fractured ceramic head or liner to a metal-on-polyethylene bearing surface secondary to third body wear from retained ceramic particles. The association of having a cobalt-containing prosthetic, an elevated marker of cobalt burden, and findings of end-organ toxicity has been coined "arthroprosthetic cobaltism" which results from cobalt-containing orthopedic implants. In India, the Medical Device regulation Rules give authority to regulate all medical devices to ensure that these products were safe and efficacious. The law created a four-tiered classification scheme; only devices that pose the most significant safety risks must meet premarket approval standards equivalent to new drugs. However, all medical devices are subject to general controls during production and after the product have entered the stream of commerce. These controls include the government's power to order recalls, notification of defects, and repair. Because of the difficulty of uncovering all device-related problems before marketing, the authority to acquire information on medical devices in the marketplace and to respond to newly discovered public health risks is a critical responsibility. The implant made of cobalt and chromium was found to be leaking metals in the body of patients, leading to fluid accumulation and cobalt and chromium metal poisoning. Like most other Heavy metals, cobalt and chromium act as multiorgan toxins, by inhibiting several key enzyme systems and interfere with initiation of protein synthesis. International Agency for Research on Cancer (IARC) consider cobalt and cobalt containing compounds possibly carcinogenic to humans. The classic toxidrome of chronic cobalt poisoning is tetrad of Goitre, Polycythemia, Cardiomyopathy and Metabolic acidosis.[1] The classic toxidrome of chronic cobalt poisoning is tetrad of Goitre: Polycythemia, Cardiomyopathy, Metabolic acidosis. Patients develop gradual hearing loss due to auditory nerve toxicity, vision loss due to cataract and optic nerve atrophy, unexpected weight gain, cardiomyopathy, Brain Stroke, dental caries, Osteosarcoma and untimely death, suggestive of chronic heavy metal toxicity due to leakage of metal from hip implants. On laboratory testing, Patients with metallic implants had elevated blood levels of chromium and cobalt ions. Further complicating the interpretation of urinary cobalt concentrations is the abundance of organic cobalt in the form of vitamin B12. A detailed vitamin supplementation history is required prior to the interpretation of a urine or blood cobalt concentration, as a diet regimen high in vitamin B12 may increase urine cobalt concentrations. For this reason, speciation of cobalt has been investigated. The ratio of inorganic to organic cobalt is higher in cobalt implanted patients (2.3) when compared to controls (1.01), independent of the wide variations of urinary cobalt concentrations. *Toxic concentrations of cobalt in serum***:** Well-functioning metal implants containing cobalt and often chromium, are usually associated with very low circulating metal concentrations. Normal serum concentrations of cobalt are frequently reported as 0.1 to 1.2 mcg/L. Concentrations above 7 ppb (7 mcg/L) are probably indicative of failing implant and may be associated with local tissue reactions. In the "arthroprosthetic cobaltism" group, serum cobalt concentrations ranged from 24 to 625 mcg/L. In contrast, several case series of metal-on-metal hip arthroplasties and resurfacings demonstrate peak serum cobalt concentration not to exceed that of 11.5 mcg/L barring one outlier of 35 mcg/L at 1 year post-procedure. Based on this data, some recommend that the risk of "arthroprosthetic cobaltism" be suspected when serum cobalt concentrations exceed 10 mcg/L.*Toxic concentrations of cobalt in urine:* Cobalt is primarily eliminated in the urine and to a lesser extent in the feces making urine cobalt evaluation most appropriate. Normal reference urine cobalt concentrations are between 0.1 and 2.2 mcg/L. In contrast, acute elemental cobalt ingestion resulted in a concentration of 1700 mcg/L on a spot urinalysis several days after the exposure. In the "arthroprosthetic cobaltism" cases, one patient had a urine cobalt concentration of 16,500 mcg/L. *Management of cobalt toxicity:* Patients with acute cobalt poisoning require aggressive therapy. In ingestion of cobalt, decontamination by gastric emptying, activated charcoal, or whole bowel irrigation. An attempt of whole-bowel irrigation for radiopaque solid forms of cobalt should be

made prior to endoscopic or surgical removal. Regardless of the decontamination procedure utilized, chelation therapy should be not be initiated until the gastrointestinal cobalt source has been removed. If there is a large stomach burden in solid form, endoscopic or surgical removal may be of benefit, keeping in mind that the administration of activated charcoal prior to surgical removal may obscure visualization of the surgical field. After decontamination, reduction of tissue burden and prevention of end-organ toxicity is the next crucial step. Succimer and EDTA (ethylenediaminetetraacetic acid) were able to enhance fecal elimination. Glutathione and DTPA (diethylenetriaminopentaacetic acid) were able to enhance urinary elimination, and NAC (N-acetylcysteine) was able to enhance elimination by both routes. NAC can reduce tissue burden and injury due to cobalt in the liver and spleen. NAC, L-cysteine, and succimer may improve survival by 40% to 50%. Ultimately, Cobalt implanted patients need to undergo urgent revision surgery for replacing cobalt implants with ceramic implants, to prevent further heavy metal toxicity, thus preventing toxic damage to their body. However, despite removal of the prosthesis and chelation therapy, the patient may develop permanent hearing loss and a persistently elevated serum concentration. This permanent hearing loss and persistently elevated serum concentration are most likely due to a delay of 7 months from onset of symptoms and metallosis of tissue to treatments. In conclusion, based on a single human case report, several animal studies and safety profiles, EDTA and NAC can be used as antidotal therapy. Indications for treatment should include patients who demonstrate end-organ manifestations of toxicity. This includes metabolic acidosis and cardiac failure. Other manifestations of severe cobalt toxicity such pericardial effusion, clinically significant goiter, and hyperviscosity syndrome should be treated aggressively with pericardiocentesis, airway protection, and phlebotomy, respectively. EDTA should be administered as doses of 1000 mg/m2/d by continuous infusion for 5 days. If the diagnosis is confirmed and signs of cardiac failure and metabolic acidosis persist after 5 days, an alternate chelator (succimer or DTPA) can be started. Similarly, NAC dosing should be based on the acetaminophen (APAP) experience. The 20 hour intravenous NAC protocol should be initiated and continued as in the case of fulminant hepatic failure for as long as the patient can tolerate therapy or continued if cardiac failure or acidemia persists. If there are contraindications to intravenous NAC, oral NAC can be administered using one of the APAP treatment regimens. Thiamine hydrochloride should be administered to all patients presenting with or without overt cardiomyopathy independent of whether the patient is alcoholic or malnourished. The dose of thiamine is not well defined but should be based on its safety and clinical experience with the treatment of Wernicke encephalopathy. The daily administration of 100 mg of parenteral thiamine can be initiated with increasing doses to 100 mg every hour for life threatening manifestations (cardiac failure and metabolic acidosis). *Legal issues in cobalt toxicity:* Metallic Hip implanted Patients, as Plaintiffs in court, claims that the companies falsely promoted the device, most commonly used to treat joint failure caused by osteoarthritis, by saying it lasted longer than similar implants that include ceramic or plastic materials. There is a deeply flawed system in place that depends on companies to self-report adverse events with their devices. Not only is there a failure to hold companies accountability for unsafe, faulty products but the utterly lax oversight can even enable purposeful negligence amounting to criminal behaviour in following up with patients.[2] Medical Device Rules (2017) have now adequate provisions to take on the companies that sell adulterated products or faulty devices in India. There are several instances where action has been taken against negligent manufacturers under these sections of D&C Rules in past. Quality has to be guaranteed during lifetime of product- in case of implant, the claimed life of implant. The high number of failure indicates substandard quality by way of product design and material used for intended purpose that caused blood poisoning due to heavy metals in high number of cases.[3] *Recent Medicolegal Cases reported due to Cobalt toxicity or hip implantsor product liability:* A Pharmacist via RTI (Right to information) challenged Hip implant Manufacturer-, for import and marketing clearance of "ASR XL Acetabular System" and "ASR Hip Resurfacing system". Central Information Commission (CIC) commented that the pharmacist has successfully made out his case that he needs this information in "larger public interest" on behalf of thousands of patients suffering in India waiting to get relief in the form of monetary compensation against the parent company. Ministry of Health and Family Welfare(MOHFW) has asked the drug regulator - Central Drug Standard Control Organisation(CDSCO) - to set up committees in states to receive complaints from patients who were affected by faulty devices. CIC ordered the CDSCO, saying the matter pertains to large number of patients who had to suffer

because of faulty products which were recalled by the United States. On being tested and found defective these implants have been banned from usage worldwide. But patients, mostly senior citizens in India, are being freely recommended and implanted with these allegedly cancer-causing devices with far reaching complications, Information Commissioner noted in the order, citing pharmacist's submissions.[4] Recently, the CDSCO, which works under the Health Ministry, put out a report on its website stating the Manufacturer "suppressed" facts on the harm caused by surgeries which were conducted on patients in India using "faulty" hip replacement systems. A group of patients, who suffered due to alleged faulty hip replacement surgeries by a multinational firm, have written to Union Health Minister, saying it is surprising that the media has been able to get the report yet the persons directly affected have been kept in the dark. Reports quoting the expert committee findings say that over 3,600 patients with faulty implants remain untraceable, and that at least four deaths have been reported among these patients.[5] After considering all the facts and details as well as taking into account the relevant literature, the committee in its report said that the ASR (articular surface replacement) hip implants manufactured, were found to be faulty, leaking toxic heavy metals into body of the patients, which resulted in higher instances of revision surgeries globally including India. The report further said, "The committee is of the considered view that the revision surgeries were necessitated due to the faulty ASR, as well as negligence of the firm in approaching the patients, and therefore it is the responsibility of the firm to compensate all the affected patients." The committee suggested that Manufacturer be made liable to pay at least Rs 20 lakh to each affected patient, and the reimbursement for revision surgeries should continue until August 2025. Manufacturer suppressed the key facts while applying for a fresh licence. As per norms, the company had to file any adverse report of the products on its patients globally.[6] In 2016, a US court had ordered Manufacturer and its Orthopedics unit to pay more than $1 billion to six plaintiffs who had sued the company for faulty hip implants. The court had found that the metal-on-metal hip implants were defectively designed and that the companies failed to warn consumers about the risks. Manufacturer had agreed to pay compensation to around 8,000 American citizens who had sued the company for its faulty devices. Covering 8,000 US patients, the settlement, announced by Manufacturer, is tipped to be the highest ever for any medical device. Manufacturer ceased selling in USA, the metal-on-metal implant devices in 2013 after the U.S. Food and Drug Administration (FDA) strengthened its artificial hip regulations. A federal jury in Dallas ordered Manufacturer and its orthopedics unit to pay $247 million to six patients who said they were injured by defective hip implants. [7] What makes the issue of compensation even more relevant is the recent news that Manufacturer was ordered to pay $4.7 billion in damages to 22 women who alleged that they got cancer after using its talcum powder. A jury in the US state of Missouri initially awarded $550million in compensation and added $4.1 billion in punitive damages. The verdict, which came out in July 2018, comes as the pharmaceutical giant battles some 9,000 legal cases involving its signature baby powder.[7] In Barker v. Lull Engineering, US courts found products defective if they fail to perform as safely as the user would expect, or if the defendant cannot prove that the benefits of the design outweigh the risks. The Restatement of Torts, a compendium of the views of leading legal scholars, recommends limiting application of these principles to products that pose generic risks—so-called "unavoidably unsafe" products — and cites vaccines and drugs as examples of such products.[8] In Beshada v. Johns-Manville Products Corp., the New Jersey Supreme Court held that a state-of-the-art defense is irrelevant for strict liability; manufacturers are responsible for failure to warn of dangers that were undiscoverable at the time of manufacture.[9] In the case involving the drug diethylstilbestrol (DES), Brown v. Superior Court, the appellate court held that strict liability does not apply to drugs with unexpected side effects. Thus, plaintiffs could only use a theory of negligence to sue the producer.[10] In West v. Johnson & Johnson, a case involving toxic shock syndrome related to the use of tampons, the court allowed the victim to use the "consumer expectation" test derived from the principles of strict liability.[11] In Wells v. Ortho Pharmaceutical Co., the court held: A cause-effect relationship need not be clearly established by animal or epidemiological studies before a doctor can testify that, in his opinion, such a relationship exists. As long as the methodology employed to reach such a conclusion is sound, products liability law does not preclude recovery until a "statistically significant" number of people have been injured or until science has had the time and resources to complete sophisticated laboratory studies of the chemical.[12] Rizzetti et al (2009) described a case of 58yr old woman who developed blindness, sensorimotor deafness and polyneuropathy after revision

of left hip arthroplasty. Cobalt and chromium concentrations in biological samples were substantially higher than the reference values: cobalt concentrations were 1187mcg/L in urine (Reference Range(RR) 0.1-1.5 mcg/L), 549 (RR 0.05-2.7) mcg/L in blood, 90 (RR 0.1-0.6) mcg/L in plasma, 11.4 (RR 0.05-2.7) mcg/L in CSF.[13] Hart AJ et al (2009) conducted study on 164 patients (101 men and 63 women), in which hip replacements were evaluated, 106 with metal on metal hips and 58 with non-metal on metal hips age <65yrs, with a perioperative diagnosis of osteoarthritis and no pre-existing immunological disorders. It was found that Circulating levels of cobalt and chromium from metal on metal hip replacement are associated with CD8+ T cell lymphopenia.[14] Feldstein et al (2016) reported a case of 61-year-old female patient presents with worsening groin pain and symptoms suggesting cobalt toxicity – including vision and hearing loss – following revision of a fractured ceramic-on-ceramic bearing surface to a cobalt-chrome-on-polyethylene bearing surface. The pain increased over the course of the year and eventually became intractable, with an associated crunching sensation within the joint. Radiographs revealed a fractured ceramic acetabular liner and evidence of radio-dense material around the hip joint. Serum cobalt level: 1,997mcg/L (normal, <2.8). Serum chrome level: 55.7mcg/L (normal, <1.8). In July 2015, the patient began to experience hearing loss followed by blurry vision, sustained sinus tachycardia, new onset diabetes insipidus, and peripheral neuropathy. By September 2015, however, X-rays of the left THA showed marked wear of the cobalt-chrome head and extensive deposition of radio-opaque debris in the effective joint space extending down the thigh. A month later, she had a dislocation during physical therapy that requiring closed reduction in the operating room. Patient was diagnosed with Cobaltism with evidence of cardiac tamponade, hypothyroidism, hearing loss, and polycythemia underwent implant removal and chelation with 2,3-dimercaptoproprane-1-sulfonate, which resulted in decreased blood cobalt concentrations but permanent hearing loss. [16] Oldenburg et al(2009) undertook a detailed cross-sectional health screen at a mean of 8 years after surgery in 35 asymptomatic patients who had previously received a metal-on-metal hip resurfacing (MoMHR) versus 35 individually age and sex matched asymptomatic patients who had received a conventional hip replacement. Study reported that Chronic exposure to low elevated cobalt concentrations in patients with well-functioning MoMHR prostheses may have systemic effects, potentially deleterious effects on left ventricular function.[17] Lumbar metal-on-metal total disk replacements are associated with smaller elevations in serum cobalt concentrations when compared to hip resurfacing or total hip arthroplasties (THR). There is matter of concern about high metal ion concentrations after metal-bearing Total Disc Replacements(TDR), as the levels appear to be only moderately elevated. However, spinal surgeons using a metal-on-metal TDR should still be aware of concerns expressed in the hip replacement literature about toxicity from elevated metal ion levels, and inform their patients appropriately.[18] Pelclova et al(2012) reported a Severe cobalt intoxication following hip replacement revision. Clinical symptoms and serum cobalt reduction responded well to arthroplasty revision and potentially chelation therapy. The key to treatment of this entity is early clinical suspicion with the constellation of findings of cardiomyopathy, hypothyroidism, polycythemia, and peripheral and central nervous system impairment. Early arthroplastic revision supports the decontamination tenets; however, emergent revisions may not be practical in an acutely ill patient. Therefore, the only modality of treatment other than supportive may be chelation. However, the single case report of DMPS treatment for a patient with "arthroprosthetic cobaltism" (including cardiomyopathy, neurologic derangements, hypothyroidism, and polycythemia) was able to demonstrate a decrease in serum cobalt concentration and an increase in urinary cobalt concentration postchelation.[19] *Personal injury lawyers search for documentary evidence:* Medical device companies that exclude e-mail in their document retention/purging policies are courting trouble. Increasingly, discovery in litigation includes requests to review e-mail records. In some cases, e-mail contains the proverbial "smoking gun" document helping a plaintiff make his or her case. These can include e-mail where a design engineer writes, "We need to re-work the design before a patient gets killed," or "A recall is much more costly than simply paying the claims." Personal injury lawyers dream about finding such documents, because they can astronomically inflate the value of a claim. Even without any such incriminating e-mails in storage tapes or hard drives, problems abound. One reason: the cost of retrieving and reviewing e-mail archives can be so onerous that companies are compelled to settle cases rather than endure the cost and time of e-mail discovery production. It is thus recommended to include e-mail in your corporate document management and destruction policy.[20] Direct-to-consumer advertising

will increase and may erode the learned intermediary defense to product liability claims. Historically, drug and device companies have successfully asserted a "learned intermediary defense" against "failure to warn" claims in product liability suits. This legal doctrine holds that drug and device companies only have a duty to warn the doctor – not the patient/consumer – of contraindications and potential complications of using a medical device. This was because typically doctors – not the patients themselves – make the buying decisions regarding medicines and medical equipment. With the increase in direct-to-consumer ads for medications such as Claritin, Flonase, and Viagra, plaintiff attorneys may argue that this defense no longer applies, that companies have waived the defense by advertising directly to consumers.

Suggestion: have legal counsel review any direct-to-consumer ads in light of promises, warranties, and its possible effect on legal defenses to liability claims. As part of prudent risk management, medical device firms should try to peek over the horizon to assess developing trends in the law, litigation, and in claim patterns. Being forewarned is being forearmed. Knowing where there are potential areas of claims may help medical device firms navigate the rocks and shoals of today's shifting tort system.[20]

CONCLUSION

Arthroprosthetic cobaltism is unique in that there is a large reservoir of metal, and the clinical presentation may be sub-acute and mistaken for other natural disease processes. The key to treatment of this entity is early clinical suspicion with the constellation of findings of cardiomyopathy, hypothyroidism, polycythemia, and peripheral and central nervous system impairment. In symptomatic Cobaltism, clinical symptoms and serum cobalt reduction respond well to chelation therapy and arthroplasty revision. However, emergent revisions may not be practical in an acutely ill patient. Therefore, the only modality of treatment other than supportive may be chelation. So, Prevention of cobalt exposure is better option, than treating the fatal outcomes of cobalt toxicity.

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