Cobalt in periprosthetic soft tissue

Observations in 6 revision cases

Courtland G. Lewis[1], Robert M. Belniak[1], Sidney M. Hopfer[2,3] and F. William Sunderman Jr[2,3]

Cobalt (Co) was analyzed in sera obtained before surgery and in biopsies of periarticular soft tissue from 7 control patients undergoing primary total hip arthroplasty and from 6 Co-exposed patients who developed aseptic loosening of the femoral component after hip arthroplasty (CoCrMo alloy, > 59 percent Co, metal-on-plastic type). Serum-Co concentrations were not elevated in the Co-exposed patients compared with control patients or healthy adults. In 5 of the 6 Co-exposed patients, Co concentrations were greatly increased in periprosthetic tissue sections 0–1 mm from the synovial surface (median 2.4 [2.1–27] μg Co/g) compared with corresponding sections from the control patients (median 0.4 [0.1–0.6] μg Co/g). Co concentrations diminished in tissue sections at successive distances of 2–3 and 4–5 mm from the synovial surfaces. In the Co-exposed patients, Co concentrations in sera and periprosthetic soft tissues were not correlated, indicating that serum Co concentration is not a reliable index of the Co burden in periprosthetic soft tissue.

Departments of [1]Orthopedics, [2]Laboratory Medicine, and [3]Pharmacology, University of Connecticut School of Medicine, 10 Talcott Notch Road, Farmington, Connecticut, CT 06032-1805, U.S.A.
Tel +203–679–6650. Fax +203–679–6649
Submitted 90-11-02. Accepted 91-06-08

Implantation of cobalt-containing alloys may possibly pose a carcinogenic risk in view of several case reports of malignant neoplasms, mostly soft tissue sarcomas, near orthopedic implants made of CoCrMo alloy (Tayton 1980, McDonald 1981, Penman and Ring 1984, Swann 1984, Weber 1986, Hughes et al. 1987, Martin et al. 1988). Evidence that alloys of cobalt, chromium, and other metals are carcinogenic in experimental animals has been reviewed by Sunderman (1989) and Jensen and Tuchsen (1990).

The goals of the present investigation were, first, to determine whether Co concentrations are increased in sera and periarticular soft tissue of patients with failed hip prostheses made of CoCrMo alloy; secondly, to test for correlation between Co concentrations in sera and periprosthetic soft tissue; and, thirdly, to assess the gradient of Co concentrations in periarticular soft tissue of patients with failed hip prostheses.

Patients and methods

This study, which was approved by the Human Experimentation Committee of the University of Connecticut Health Center, included two groups of patients. The Control Group consisted of 7 patients with severe degenerative (nonrheumatoid) arthrosis of the hip (4 women, 3 men; aged 57 to 79 years) undergoing primary total hip plasty. Prior to the operation, these patients did not have any implanted prostheses. The Exposed Group consisted of 6 patients (3 women, 3 men, aged 28 to 76 years) who had undergone unilateral total hip arthroplasty 3 to 13 years previously and had developed aseptic loosening of the femoral component, necessitating its replacement. The failed prostheses were all fabricated of CoCrMo alloy (ASTM F75-82, containing > 59 percent Co, 27–30 percent Cr, 5–7 percent Mo, 1 percent Mn, 1 percent Si, < 1 percent Ni, < 0.75 percent Fe, and 0.35 percent C); there were three TR-28 prostheses, one Harris-precoat prosthesis, one Charnley-Müller prosthesis, and one HD-2 bipolar prosthesis (Table 1). These devices were all of the metal-on-plastic type, having a polyethylene acetabular cup; the prostheses had been fixed with polymethylmethacrylate. The control and exposed patients denied any occupational or environmental contacts with Co compounds or Co-containing alloys.

Blood samples were obtained on the day before surgery with stringent precautions to avoid metal contamination (Sunderman et al. 1988). Serum specimens were analyzed for Co by electrothermal atomic absorption spectrophotometry (EAAS; Sunderman et al. 1989) using an automated analyzer with Zeeman background correction (model 5000-Z, Perkin-Elmer, Inc., Norwalk, CT, U.S.A.).

Table 1. Cobalt concentrations in sera and periarticular soft tissues of patients with hip prostheses

Case	Age	Sex	Failed prostheses	Duration of implantation	Serum Co concentration	Tissue Co concentrations (mg/g, wet wt) at specified distances from the synovial surface		
				months	mg/L	0–1 mm	2–3 mm	4–5 mm
1	68	M	'Harris pre-coat'	33	< 0.02	26.6	20.8	0.90
2	70	M	Type 'TR-28'	79	0.08	2.52	1.48	1.02
3	55	F	Charnley-Müller	158	0.08	2.42	1.62	1.07
4	76	F	Type 'TR-28'	135	< 0.02	2.28	0.84	0.72
5	28	F	'HD-2 bipolar'	98	0.08	2.09	1.52	1.08
6	85	F	Type 'TR-28'	41	< 0.02	0.58	0.29	0.18
All the patients,				median	0.05	2.35*	1.50*	0.96*
				min	< 0.02	0.58	0.29	0.18
				max	0.08	26.6	20.8	1.08
Seven control patients with primary hip arthroplasty, 3 males, 4 females, aged 57–79 yrs				median	0.05	0.37	0.06	0.07
				min	< 0.02	0.09	0.04	0.02
				max	0.11	0.60	0.14	0.17
Healthy adult volunteers (Sunderman et al. 1989), 21 males, 21 females, aged 26-68 yrs				median	0.05			
				min	< 0.02			
				max	0.25			

*$P < 0.01$ vs corresponding values in control patients.

At surgery, a full-thickness specimen (~2 cm diameter) of hip capsule (Control Group) or pseudocapsule (Exposed Group) was excised from the anterior aspect of the hip joint. The synovial surface of the tissue specimen was marked with a silk suture, and the specimen was placed in a sterile, metal-free plastic cup. After surgery, the tissue specimen was trimmed into a disk (1.2 cm diameter) and pressed with a syringe plunger into the cylinder of a polyethylene syringe (10 mL volume, 1.2 cm internal diameter) so that the synovial surface faced the surface of the plunger. The syringe containing the tissue specimen was kept frozen at –20 °C until 20 min prior to sectioning the tissue. The disk of frozen tissue was sectioned with a motorized slicing machine (model 5406, Globe, Inc., Springfield, MA, U.S.A.), adjusted to cut slices 1 mm thick. The initial slice (0–1 mm from the synovial surface), the third slice (2–3 mm from the synovial surface), and the fifth slice (4–5 mm from the synovial surface) were weighed, digested with a mixture of nitric, sulfuric, and perchloric acids, and analyzed for Co by EAAS (Sunderman et al. 1988, 1989). Adjacent tissue samples were fixed in formalin and processed for examination by light microscopy.

Comparisons of Co concentrations in specimens of serum and tissue from control versus exposed patients were performed with the Mann-Whitney *U*-test and Spearman's correlation test (Sachs 1984). Statistical analyses of Co concentration gradients in periarticular tissue specimens were performed using Wilcoxon's signed-ranks test (Sachs 1984) and the trend test of Tukey et al. (1985).

Results

On the day before surgery, the median cobalt concentration in sera of the 6 Co-exposed patients was 0.05 (< 0.02–0.08) μg/L, which did not differ from the corresponding values in the 7 control patients. Serum Co concentrations in the Co-exposed and control patients were all within the reference range for healthy adults (Sunderman et al. 1989).

In specimens of periarticular soft tissue from the control patients, Co concentrations were slightly higher in the superficial layer than in the underlying layers (Table 1). Compared with these control values, Co concentrations were markedly elevated in specimens of periarticular soft tissue from the 6 patients with failed hip prostheses ($P < 0.01$). The tissue Co accumulation in these Co-exposed patients was consistently greater in the superficial layer than in the successive underlying layers ($P < 0.01$). Even at 4–5 mm from the synovium, tissue Co concentrations were significantly higher in exposed patients than in control patients ($P < 0.01$).

No correlation was found between the paired values for Co concentrations in sera and periprosthetic tissue specimens of patients with failed hip prostheses regardless of the distance from the implant. Histologic examination of periarticular tissue specimens from the Co-exposed patients consistently showed a fibrous pseudomembrane with chronic inflammation. Foreign body giant cells were prominent in the biopsy of Case 3. Intracellular inclusions suggestive of polyethylene wear debris were seen in most of the biopsies.

Discussion

The instruments used in this study for primary or revision arthroplasty and for cutting tissue specimens were made of several AISI (American Iron and Steel Institute) grades of stainless steel. Analyses of tissue Cr concentrations were not attempted, because, according to industry specifications, the Cr content of the AISI steels range from 16–18 percent, and it was deemed impossible to prevent Cr contamination of the specimens. On the other hand, the Co content of the steels is < 0.1 percent, and preliminary trials did not disclose Co contamination when animal tissues were sectioned with a scalpel and the slicing machine. In another pilot experiment, measurements of the recovery of Co added in vitro to tissue samples ranged from 93 to 105 percent. Hence, our analyses of tissue Co concentrations are as reliable as can presently be achieved under clinical conditions. The finding that Co concentrations in periarticular soft tissue from control subjects were slightly higher in sections near the synovial surface than in deeper layers suggests that Co accumulates in the synovium. However, traces of Co-containing dust from the operating room environment might conceivably have contaminated the synovial surface of the tissue samples.

Studies in experimental animals with CoCrMo implants have shown that constituent metals are slowly released, leading to their accumulation in surrounding tissues (Ferguson et al. 1962, Woodman et al. 1983, 1984). Gradual mobilization of metals from CoCrMo prostheses has also been documented in patients, based upon analyses of Co or Cr concentrations in serum or urine (Coleman et al. 1973, Miehlke et al. 1981, Pazzaglia et al. 1986, Sunderman et al. 1989) and detection of Co or Cr in periprosthetic soft tissues and distant organs (Emnéus et al. 1961, Michel et al. 1984, 1991). The release of metals from implanted prostheses metal has been attributed to corrosion, wear, or a combination of these factors. In our study, the Co-exposed patients all had revision surgery as a consequence of aseptic loosening of a cemented femoral component. The fretting action of the metal against bone, augmented by three-body wear from cement and acrylic particles, probably contributed to the local release of metals (Mirra et al. 1976, McKellop et al. 1981, 1990).

Michel et al. (1984) used neutron activation analysis to measure the concentrations of Co and other elements in full-thickness specimens of articular capsule from 26 control patients who underwent primary hip arthroplasty and from 36 exposed patients who underwent revision arthroplasty because of loosening of CoCrMo hip prostheses that had been implanted for 4 to 124 months. The Co concentrations in periarticular tissue specimens from the control and exposed patients averaged (as geometric means) 0.05 and 2.03 µg/g dry weight, respectively, which are consistent with our results. Michel et al. (1984) did not analyze Co concentrations in serum or measure the gradient of Co accumulation in periarticular tissue, but they did note that Co concentrations in specimens of fascia lata, sampled 4 to 6 cm from the hip joint, averaged 0.15 and 0.11 µg/g dry weight, respectively, in the two groups of patients.

Our study documented a gradient of Co concentrations in periprosthetic soft tissue specimens from Co-exposed patients with failed hip prostheses. Despite the elevated tissue Co burdens, Co concentrations were not elevated in serum. Thus, the finding of normal Co concentration in a patient's serum does not signify that the Co concentration is normal in the periprosthetic tissue. Although serum Co concentrations were previously found to be elevated in some patients with aseptic loosening of CoCrMo joint prostheses (Miehlke et al. 1991, Sunderman et al. 1989), our study does not support the suggestion that serum Co concentrations could serve as a diagnostic index of Co burdens in periprosthetic tissues of orthopedic patients (Sunderman 1990).

Our finding that patients with failed CoCrMo hip prostheses have a gradient of Co concentrations in periprosthetic soft tissue provides additional clinical evidence that Co is released from failed prostheses and accumulates locally. Because Co powder and $CoCl_2$ have been reported to induce soft-tissue sarcomas following parenteral administration to rats (Heath 1956, Shabaan et al. 1977), it is arguable that cobalt deposited in patients' tissues could pose a carcinogenic hazard. Therefore, we endorse the current initiative to establish a worldwide registry of tumors that arise near replaced joints, as communicated by orthopedic surgeons throughout the world (Apley 1989). This effort should be designed to ascertain whether any association between loosening or corrosion of joint replacements and local malignancies is related etiologically or is purely coincidental, and, if a causal relationship is found, to estimate the incidence of such malignancies.

Acknowledgements

The authors are grateful to Marilyn Folcik, R.N., M.P.H., for assisting in patient management; Linda Ziebka, M.S., for performing the Co analyses; Faripour A. Forouhar, M.D., for histopathologic consultations; Trudy Lerer, B.S., for statistical consultations; and Harry R. Gossling, M.D., for helpful advice and suggestions. This study was supported by a grant to Dr. Sunderman from Northeast Utilities, Inc.

References

Apley A G. Malignancy and joint replacement: the tip of an iceberg? (editorial). *J Bone Joint Surg* (Br) 1989; 71 (1): 1.

Braun E, Schmitt D, Nabet F, Legras B, Coudane H, Molé D. Urinary concentration of cobalt and chromium in patients with a non-cemented total hip prosthesis. *Int Orthop* 1986; 10 (4): 277–82.

Coleman R F, Herrington J, Scales J T. Concentration of wear products in hair, blood, and urine after total hip replacement. *Br Med J* 1973; 1 (852): 527–9.

Emnéus H, Stenram U, Baecklung J. An X ray spectrographic investigation of the soft tissue around titanium and cobalt alloy implants. *Acta Orthop Scand* 1961;30: 226–36.

Ferguson A B, Akahoshi Y, Laing P G, Hodge E S. Characteristics of trace ions released from embedded implants in the rabbit. *J Bone Joint Surg* (Am) 1962; 44: 323–36.

Heath J C. The production of malignant tumours by cobalt in the rat. *Brit J Cancer* 1956; 10: 668–73.

Hughes A W, Sherlock D A, Hamblen D L, Reid R. Sarcoma at the site of a single hip screw. A case report. *J Bone Joint Surg* (Br) 1987; 69 (3): 470–2.

Jensen A A, Tuchsen F. Cobalt exposure and cancer risk. *Crit Rev Toxicol* 1990; 20 (6): 427–37.

Martin A, Bauer T W, Manley M T, Marks K E. Osteosarcoma at the site of total hip replacement. A case report (published erratum appears in J Bone Joint Surg (Am) 1989 Aug; 71 (7): 1112). *J Bone Joint Surg* (Am) 1988; 70 (10): 1561–7.

McDonald I. Malignant lymphoma associated with internal fixation of a fractured tibia. *Cancer* 1981; 48 (4): 1009–11.

McKellop H, Clarke I, Markolf K, Amstutz H. Friction and wear properties of polymer, metal, and ceramic prosthetic joint materials evaluated on a multichannel screening device. J *Biomed Mater Res* 1981;15: 619–53.

McKellop H A, Sarmiento A, Schwinn C P, Ebramzadeh E. In vivo wear of titanium alloy hip prostheses. *J Bone Joint Surg* (Am) 1990; 72: 512–7.

Michel R, Hofmann J, Löer F, Zilkens J. Trace element burdening of human tissues due to the corrosion of hip joint prostheses made of cobalt chromium alloys. *Arch Orthop Trauma Surg* 1984; 103 (2): 85–95.

Michel R, Nolte M, Reich M, Löer F. Systemic effects of implanted prostheses made of cobalt chromium alloys. *Arch Orthop Trauma Surg* 1991; 110 (2): 61–74.

Miehlke R, Henke G, Ehrenbrink H. Kobalt und Chrom konzentration in der Synovialflüssigkeit und im Blutserum nach Implantation von Kniegelenksendoprosthesen mit Hilfe der Neutronenaktevierungsanalyse. *Z Orthop* 1981; 119: 767–8.

Mirra J M, Amstutz H C, Matos M, Gold R. The pathology of the joint tissues and its clinical relevance in prosthesis failure. *Clin Orthop* 1976;117: 221–40.

Pazzaglia U E, Minoia C, Gualtieri G, Gualtieri I, Riccardi C, Ceciliani L. Metal ions in body fluids after arthroplasty. *Acta Orthop Scand* 1986; 57 (5): 415–8.

Penman H G, Ring P A. Osteosarcoma in association with total hip replacement. *J Bone Joint Surg* (Br) 1984; 66 (5): 632–4.

Sachs L. *Applied statistics: A manual of techniques*. Springer Verlag, New York, 2nd ed 1984: 293–403.

Shabaan A A, Marks V, Lancaster M C, Dufeu G N. Fibrosarcomas induced by cobalt chloride ($CoCl_2$) in rats. *Lab Anim* 1977; 11 (1): 43–6.

Sunderman F W Jr. Carcinogenicity of metal alloys in orthopedic prostheses: clinical and experimental studies. *Fundam Appl Toxicol* 1989; 13 (2): 205–16.

Sunderman F W Jr. Biological monitoring of metal exposures from joint implants: Clinical and experimental studies. In: *Technical principles, design and safety of implants* (Eds. Willert H G, Buchhorn G H) Huber Verlag, Bern. In press.

Sunderman F W Jr, Hopfer S M, Crisostomo M C. Nickel analysis by atomic absorption spectrometry. *Meth Enzymol* 1988; 158: 382–91.

Sunderman F W Jr, Hopfer S M, Swift T, Rezuke W N, Ziebka L, Highman P, Edwards B, Folcik M, Gossling H R. Cobalt, chromium, and nickel concentrations in body fluids of patients with porous coated knee or hip prostheses. *J Orthop Res* 1989; 7 (3): 307–15.

Swann M. Malignant soft tissue tumour at the site of a total hip replacement. *J Bone Joint Surg* (Br) 1984; 66 (5): 629–31.

Tayton K J. Ewing's sarcoma at the site of a metal plate. *Cancer* 1980; 45 (2): 413–5.

Tukey J W, Ciminera J L, Heyse J F. Testing the statistical certainty of a response to increasing doses of a drug. *Biometrics* 1985; 41 (1): 295–301.

Weber P C. Epithelioid sarcoma in association with total knee replacement. A case report. *J Bone Joint Surg* (Br) 1986; 68 (5): 824–6.

Woodman J L, Black J, Nunamaker D M. Release of cobalt and nickel from a new total finger joint prosthesis made of vitallium. *J Biomed Mater Res* 1983; 17 (4): 655–68.

Woodman J, Shinn W, Urban R, Galante J. Electron microprobe analysis of metal ion transport in cortical bone. *J Biomed Mater Res* 1984; 18 (4): 463–6.