

Preventing metabolic consequences of ischemia

Tissue acidosis due to accumulated lactate, a major cause of delayed neuronal injury, results when ischemia precludes aerobic metabolism of glucose. Therefore, intravenous solutions should not contain glucose, glucose levels should be monitored frequently, and hyperglycemia should be controlled aggressively.

Calcium homeostasis is disturbed during ischemia, leading to increased calcium influx, membrane degradation, release of arachidonic acid, vasoconstriction, and platelet aggregation. Free radicals are also released, producing additional membrane damage. Therapeutic interventions at this level would include antagonists of the excitatory neurotransmitters, calcium-channel antagonists, membrane-stabilizing agents, free-radical scavengers, prostacyclin, platelet antiaggregants, and vasodilators that selectively affect the arterioles.

Cerebral edema due to cellular swelling and fluid extravasation across a disrupted blood-brain barrier further impedes cerebral blood flow and clearance of lactate. This is an ominous sign, best treated in an intensive care unit with intracranial pressure monitoring and osmotic dehydration.

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HEALTH EFFECTS OF MAN-MADE MINERAL FIBERS

Man-made vitreous fibers, used everywhere in modern society as insulation, filters, and reinforcers for plastic, have only recently been subjected to studies in animals and man to determine their safety. Fortunately, their health risk appears to be low and can be minimized by controlling airborne exposure through ventilation (the recommended expo-

sure limit is one fiber per cm³) and proper work practices (eg, use of respiratory protection).

What is the pathogenic potential of these fibers? What are the short-term and long-term occupational risks associated with their manufacture? What are the clinical signs of exposure? The following brief update for clinicians addresses the key concerns about these widely used materials.

FIBER TOXICOLOGY

Man-made vitreous fibers can be divided into three general groups: glass fiber, mineral wool, and ceramic fiber. They have played an increasingly important role in recent years as asbestos substitutes.

Three main factors determine the pathogenic potential of a fiber: the dose delivered to the target organ, the dimensions of the fiber, and its durability in biologic systems. The chemical composition and surface properties of the fiber may also contribute to its disease-producing potential. Dose is related to airborne exposure to respirable fibers, measured in fibers per cm³. Some fibers clear the mucociliary mechanism, while others are translocated to respiratory or terminal bronchioles, the interstitium, and the lymphatic system.

According to the Stanton hypothesis, long, thin fibers ($\leq 0.25 \mu\text{m}$ in diameter and $> 8 \mu\text{m}$ in length) are more carcinogenic than shorter, thicker fibers. Asbestos fibers tend to fracture lengthwise, making them more dangerous than man-made vitreous fibers, which fracture crosswise. The probability of disease increases the longer a biologically active fiber remains unaltered. Fibers fracture and dissolve in biologic systems; in vitro testing with Gamble's solution reveals that, among man-made fibers, refractory ceramic fiber is the most durable, followed by mineral wool and glass fiber.

HEALTH EFFECTS

Concerns about the possible health effects of man-made vitreous fibers are based on previous experience with asbestos, a well-established cause of mesothelioma, lung cancer, and both interstitial and pleural fibrosis.

Animal studies

Except for refractory ceramic fiber, most man-made mineral fibers have not caused cancer in animal studies. However, mesotheliomas can be induced

by intrapleural or intraperitoneal injection, a technique that bypasses the usual defense mechanisms and therefore is of questionable relevance. Single- and multiple-dose inhalation studies have shown that refractory ceramic fiber can induce pleural and pulmonary fibrosis, pulmonary neoplasia, and mesothelioma at the maximum tolerated dose of 250 to 300 fibers per cm^3 . The level of no observable effects was determined to be 25 fibers per cm^3 .

Irritant effects

Most workers experience skin irritation within 2 weeks of exposure. Improvement occurs with further exposure ("hardening"), but as many as 5% of workers may leave their jobs. The skin irritation characteristically consists of intense itching without significant objective findings; it is a form of mechanical irritation, not allergic sensitization. Risk factors include exposure to fibers larger than $5.3 \mu\text{m}$ in diameter, hot humid weather, and underlying skin disease. The diagnosis is based on a history of exposure, the disparity between severity of itching and objective findings, and the "cellophane tape test", where cellophane tape is pressed against the skin and examined under the microscope for fibers.

Workers can prevent irritation by wearing long-sleeved, loose-fitting work clothes and changing them frequently. Work clothes should be laundered separately from family clothes. Irritation of the eyes, nose, and throat is uncommon except with unusually dusty conditions and can be prevented with appropriate ventilation and approved respiratory protection.

Respiratory morbidity studies

No consistent pattern of respiratory effects has been noted in cross-sectional health surveys to date. One study demonstrated a 3.5% prevalence of increased interstitial markings among exposed workers, which was associated with age, length of employment, and smoking.

Mortality studies

Marsh and coworkers conducted a retrospective cohort mortality study involving over 16 000 workers in 17 glass-fiber and mineral-wool plants in the United States and found a statistically significant 8% excess in all malignant neoplasms and a 12% excess in lung cancer. The excess was greatest in mineral-wool workers but was not associated with duration of exposure. Mesothelioma deaths were within the expected range.

Simonato and coworkers conducted a historical cohort study of 25 000 workers in 13 fiber and mineral plants in Europe. Compared with the standard mortality ratio, the lung cancer mortality rate was 25% greater in the entire cohort and 70% greater in workers in whom more than 30 years had elapsed since first exposure, and these differences were statistically significant. The highest risk was in mineral-wool plants that used slag from copper refining. There were no increased rates of other cancers or nonmalignant respiratory disease. The authors speculated that employment in the early phase of fiber production may have involved exposure to higher fiber levels. Also, slag contamination with arsenic and exposure to other carcinogens (eg, polycyclic aromatic hydrocarbons from furnaces) may have been contributing factors.

Refractory ceramic fiber studies

In a multi-industry cross-sectional study of 742 workers at plants that manufacture refractory ceramic fibers, production workers had a greater prevalence of certain respiratory symptoms (eg, dyspnea) than other, unexposed employees. Pulmonary function tended to decline with increasing duration of employment, although the magnitude of this decline was small. Pleural plaques were seen in 2.4% of all production workers.

An expanded study of 801 current and former employees of a single manufacturer showed an increased prevalence of several respiratory symptoms among production workers. Both smokers and non-smokers had decreases in pulmonary function with increasing ceramic fiber exposure, but these changes were worse in smokers. The decline in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) in smokers was not clinically significant over the short term.

The overall prevalence of pleural plaques was 3.1%. However, 12.5% of workers in whom more than 20 years had elapsed since first exposure had pleural plaques, as did 26.3% of workers with more than 20 years of total exposure. A progressive relationship between cumulative exposure and the development of plaques was present. A case-control study showed a biologically plausible latent period between initial refractory ceramic fiber exposure and subsequent development of pleural plaques. Past asbestos exposure did not account for the observed association between refractory ceramic fibers and pleural plaques.

Only 46 workers had died, and the statistical power to detect a significant increase for any specific cause of death was low (eg, 0.60 for a threefold increase in lung cancer). However, no overall increase in mortality was seen for all causes of death, all cancer deaths, or any specific cause of death. There were no cases of mesothelioma.

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GLAUCOMA THERAPY: IMPLICATIONS FOR THE INTERNIST

Although treating glaucoma is the province of the ophthalmologist, internists should be familiar with the glaucoma medications their patients may be taking, since even topical agents can cause systemic side effects. Conversely, oral medications given for other conditions can affect the intraocular pressure.

SIDE EFFECTS OF GLAUCOMA DRUGS

Topical agents

Topical beta blockers can cause all the side effects of oral beta blockers: exacerbation of asthma or chronic obstructive pulmonary disease, congestive heart failure, sinus bradycardia, heart block, depression, confusion, impotence, masking of symptoms of hypoglycemia, and exacerbation of myasthenia gravis. Conversely, oral beta blockers given for high blood pressure or angina can reduce intraocular pressure. The nonselective topical beta

blockers (timolol, levobunolol, metipranolol, carteolol) tend to control intraocular pressure better than the selective beta blocker betaxolol, but the latter is safer for patients with asthma or obstructive lung disease.

The nonselective adrenergic agonists epinephrine and dipivefrin can cause hypertension, angina, tachycardia, palpitations, headaches, and tremor, in addition to the ocular complications of blurred vision (due to pupil dilation) and chronic red eye.

Topical cholinergic agonists (pilocarpine, carbachol, echothiophate, demecarium, physostigmine) are infrequently used, but they can increase gastrointestinal motility, salivation, and respiratory secretions. The anticholinergic agents (atropine, homatropine, scopolamine, cyclopentolate, tropicamide) can cause dry mouth, a flushed feeling, tachycardia, and atonic bowel.

The alpha-2 adrenergic agonist apraclonidine does not cause systemic complications, but it can cause lid elevation, conjunctival blanching, and pupil dilation.

Patient education

Systemic absorption of topical ophthalmologic medications can be minimized by instructing the patient to occlude the lacrimal sack when applying eye drops, to close the eye immediately afterward and to immediately blot up any excess fluid.

Oral agents

The oral carbonic anhydrase inhibitors (acetazolamide, methazolamide, dichlorphenamide) frequently cause potentially severe side effects: rash, fatigue, malaise, anorexia, weight loss, paresthesia, dysesthesia, depression, impotence, gastritis, renal calculi (with acetazolamide), and aplastic anemia. They increase excretion of bicarbonate and can cause metabolic acidosis, hypokalemia (especially when used with potassium-wasting diuretics), and hyperchloremia. These agents can aggravate gastritis or peptic ulcer disease. Methazolamide is metabolized in the liver and should be avoided in patients with hepatic failure.

The oral osmotic agents (glycerine, isosorbide) can cause nausea, vomiting, severe headache, dehydration, severe systemic fluid shifts, and subarachnoid hemorrhage; glycerine can cause severe glucose overload in diabetes mellitus. These agents and the intravenous osmotic diuretic mannitol are rarely used.