Salicylate-Induced Pulmonary Edema: A Complication Of Chronic Aspirin Therapy

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The presentation and management of the acute metabolic effects of salicylate intoxication are well known.[1] Not so widely recognized is the potential for the development of noncardiogenic pulmonary edema and the adult respiratory distress syndrome from chronic (and, less often, acute) salicylate ingestion.

Case Report

A 36-year-old man who smoked three packs of cigarettes per day and habitually smoked varying amounts of marijuana experienced the onset of insomnia and persistent headaches when he abruptly discontinued clomipramine therapy.

He medicated his headache according to his own "usual" treatment protocol: three to four aspirin tablets as one dose, then an increased amount with each successive dose until relief was obtained. Unable to abort the headache, the escalation in dosage continued for 7 days despite his noticing from the 3rd day of this course increasing headache, tinnitus, hearing loss, and tachypnea. He stopped the daily dosage increases only when he ran out of aspirin, about 24 hours before admission to the hospital. On this last day of ingestion he took approximately fifteen 325-mg aspirin tablets per dose between 10 and 20 times during 24 hours. In all, he consumed "about two large bottles"; from the patient's admittedly hazy recollection, it can be estimated that his total ingestion was approximately 500 tablets during the 7 days.

The patient was brought to the hospital by friends who noticed increasing confusion and slurred speech during the previous 2 days. Upon arrival in the emergency department he was disoriented, diaphoretic, pale, and dehydrated. His respiratory rate was 40/min, and his heart rate, 133 beats per minute. Laboratory data included a white cell count of 24,700/mm^3 with normal differential, normal electrolyte levels except for a total of carbon dioxide of 11 mEq/L, and a salicylate level of 38.7 ng/dL. The urine and serum screening tests for commonly prescribed and illicit psychoactive agents were negative except for the elevated salicylate level. Arterial blood gasses were pH 7.27, PCO_2 17 mmHg, PO_2 70 mmHg, and calculated bicarbonate 8 mEq/L. A chest radiograph showed slight bilateral infiltrates.

The patient was given an intravenous solution containing 5 percent dextrose and 150 mEq of sodium bicarbonate for 3 hours. With this therapy arterial blood gases changed to pH 7.50, PCO_2 18 mmHg, PO_2 56 mmHg, and bicarbonate 14 mEq/L. Despite the patient's subjective improvement in respiration, rales developed bilaterally, and increasing volumes of supplemental oxygen were required to maintain adequate oxygen saturation.

Twelve hours after admission a chest radiograph showed marked perihilar and lower lobe infiltrates, and rales were more prominent. A pulmonary artery catheter was placed to confirm the clinical suspicion of a noncardiac origin of the pulmonary edema; central venous pressure was 2 mmHg and wedge pressure was 8 mmHg. Cardiac output was normal. Despite his deteriorating respiratory status, the patient's sensorium returned to normal during this period.

As measured by serial chest radiographs, the pulmonary edema continued to worsen during the following 24 hours, but adequate hemoglobin saturation was maintained with 70 percent oxygen by mask.

Clinical improvement became obvious about 36 hours after admission, and the patient's oxygen requirements rapidly decreased. By the 4th day after admission, the patient was asymptomatic and showed no sign of illness on examination. The following morning his chest radiograph was entirely clear, and he was discharged. On sub-

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sequent outpatient visits he appeared free of residual effects of this event.

Literature Review

Pathogenesis

Pulmonary edema as a clinical feature of salicylate intoxication was first reported in 1950. A noncardiogenic cause was established in the mid-1970s by pulmonary artery catheterization.[2]

Subsequent human and animal studies have implicated an increase in pulmonary capillary permeability as the proximate cause. The reason for this change, however, is still speculative. There are three leading theories[3]: (1) aspirin inhibits prostacyclin, which normally acts to reduce capillary membrane permeability; (2) the effect is mediated by changes in platelet-vessel interaction; and (3) as in the phenomenon of neurogenic pulmonary edema, there could be a catecholamine surge induced by mild cerebral edema, leading to increased pulmonary vascular pressures.

Incidence

One study found that 22 percent of adult patients (8/36) with salicylate levels greater than 30 mg/dL developed evidence of pulmonary edema.[4] Chapman and Proudfoot[5] reported 97 cases in which patients had either survived a salicylate level greater than 70 mg/dL or died, and 6 (6.2 percent) developed pulmonary edema (one of which was probably cardiogenic). In another retrospective study 59 percent of cases of fatal salicylate ingestion had autopsy evidence of pulmonary involvement, primarily edema.[6] By contrast, in cases of clinically unrecognized salicylate intoxication, only 10 percent of patients had pulmonary edema.[7]

The rate of pulmonary edema complicating salicylate intoxication in children is unclear. Before 1985 only two cases had been reported.[3] In the Walters, et al.[3] study of 55 pediatric patients, none developed pulmonary edema. Fisher, et al.,[8] however, reported two additional cases of pulmonary edema, both fatal, among his 20 pediatric patients with salicylate intoxication.

Risk factors for the development of pulmonary edema have been described: increased age, concurrent medical illnesses, cigarette smoking, and chronic (rather than acute) intoxication.[2] There have been no case reports with salicylate levels less than 30 mg/dL, but when levels exceed this threshold, there is apparently no correlation between the serum drug level and the likelihood of developing pulmonary edema.

It is likely that this syndrome goes undetected in many patients because the tachypnea of pulmonary edema is mistaken for that commonly caused by the direct stimulation of aspirin on the respiratory drive.

Clinical Features

Salicylate-induced pulmonary edema is indistinguishable by physical examination from other causes of pulmonary edema. With salicylate poisoning, however, mental functioning is usually deranged, with nearly all patients experiencing obvious confusion or somnolence. The signs and symptoms can be evident initially or develop during the first 24 hours of observation. Pulmonary artery catheterization will typically indicate normal cardiac performance and central vascular pressures. Metabolic acidosis is commonly associated with salicylate-induced pulmonary edema, whereas respiratory alkalosis is the most common acid-base disturbance in cases without pulmonary edema.[3]

Clinical Course

In Heffner and Sahn's study,[4] patients had a mean hospital stay of 14 days. Clinical and radiographic improvement occurred within 1 to 7 days. Four of 8 patients developed adult respiratory distress syndrome and required mechanical ventilation, but all recovered. One of Walters', et al.[3] 6 patients and 2 of Chapman and Proudfoot's[5] 6 patients died. There are several individual fatalities reported in the medical literature, but the mortality rate from this condition cannot be determined from such reports. Fortunately, complete recovery appears to be the rule.

Treatment

Salicylate toxicity itself is treated in the standard fashion, with supportive care and measures to reduce further absorption and to enhance elimination of the drug.[1] The ingestion of other toxic substances, especially acetaminophen, must be suspected and treated appropriately. Respiratory support is graded to the patient's evolving needs. Volume contraction is common in salicylate intoxication and should be corrected with intravenous fluids without inducing overload. Hemo-

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dialysis has been used in too few cases to judge its efficacy, but it should certainly be considered if the salicylate level is very high (> 100 mg/dL) or if the patient's condition deteriorates despite other therapy. Maintenance of blood pH in the normal range is critical; a pH drop from 7.4 to 7.2 will double the fraction of salicylate present in the more toxic nonionized state.[3]

Prevention

Aspirin is one of the commonest causes of single-drug overdose fatalities in both children and adults. Prevention in children depends primarily on general measures to make medications physically inaccessible and on parental education about using acetaminophen in preference to aspirin for most indications in children.

The adult patients most at risk for developing pulmonary complications of toxic levels are the elderly taking large daily therapeutic doses. Prescribing physicians must be aware of the nonlinear kinetics of aspirin,[9] its drug interactions, the potential for accidental elevation of serum levels by concomitant use of other over-the-counter medications (especially mixtures that could contain additional salicylates), and the unreliability of tinnitus as a warning sign in presbycusic patients.[10]

Conclusion

Pulmonary edema is increasingly recognized as a serious complication of salicylate intoxication, especially with chronic ingestion. Fortunately, it can usually be prevented by careful patient education and treated successfully without long-term sequelae.

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