

RESEARCH ON MAGNESIUM SILICATES TOXICOLOGICAL RESPONSE IN PULMONARY FUNCTION AND IN BLOOD CIRCULATION

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Abstract

Talc (magnesium silicate) is a widely used, generally considered benign substance. It is principally used as an inert filler material in drug tablets or as a drying ingredient in baby powders. However, in both cases inappropriate use can lead to severe pulmonary toxicological responses. On the hand, intravenous injection of 'solubilized', CNS active pills can produce microemboli in small pulmonary vessels. This can lead to various degrees of granuloma formation, compromised pulmonary function, or death. Overzealous application of baby powder can also produce severe pulmonary complications if the infant inspires the powder. Although the data are relatively scarce, a number of reports suggest the existence of a chronic problem in this area.

Key words: Blood circulation, magnesium silicates, toxicology, pulmonary

INTRODUCTION

Talc (hydrous magnesium silicate: $\text{Mg}_3\text{Si}_4\text{O}_{10}[\text{OH}]_2$) is a mineral widely distributed, geologically, in various parts of the world. When mined, it often contains contaminating minerals such as crystalline silica and tremolite asbestos, which contribute to pulmonary damage in miners. Pulmonary disease has also been reported following in the inhalation of talc in non-miners. For decades, talc's most popular consumer use has been as the principal component in baby powder for the treatment of diaper rash. Its alleged utility is due to its smoothing and lubricating properties. In addition to its use by general public, talc has also been utilized by the pharmaceutical industry as an excipient in the manufacture of oral tablets as well as by the illicit drug market as a filler. When used in either baby powder, oral tablets, or street drugs, talc proven to have particular toxicological significance for the lungs when inhaled or administered intravenously.

Four categories of pulmonary disease associated with talc have been described. In certain cases, the toxicity of talc may be exacerbated by the presence of contaminating minerals, while in others, talc alone is solely involved. For example, (a) talcosilicosis is caused by the inhalation of talc mined with a high silica content. Clinical findings resulting from

talcosis resemble closely those of silicosis. Similarly, (b) talcasbestosis closely resembles asbestosis both pathologically and radiologically. On the other hand, (c) inhalation of pure talc can result in the production of chronic bronchitis, interstitial inflammations, or granuloma formation (talcosis). Finally, (d) the intravenous administration of talc-containing oral medication can lead to the production of pulmonary vascular granulomas. The latter two categories will be the subject of this review of selected articles.

INHALATION

Historically, baby powder has generally been considered innocuous and has been routinely used by mothers and nurses for the treatment of diaper rash. However, talc is not inert, particularly when in contact with exposed tissue. Over 50 years ago Antopol suggested that granuloma formation at surgical wound sites might be the result of talc transfer from surgical gloves. The irritant potential of talc is further illustrated by its use as a sclerosing agent in the treatment of pleural effusion, when it is directly applied to the pleural cavity.

Recently, both the efficacy of talc as an absorptive, odor-covering, friction-reducing agent and its safety have been questioned. This is particularly significant since powders, such as talc, have been reported to be not likely non-physical hazard associated with diaper changing. Today, concern for the most common non-occupational inhalation toxicity from talc is the inhalation of baby powder by infants.

Magnesium silicate is toxicologically benign if ingested. In fact, magnesium trisilicate has been used as an antacid as well as an effective gastrointestinal adsorbent to protect ulcerated mucosal surfaces. However, if talc is taken in via the airway, it acts as a pulmonary irritant. Symptoms observed in acute talc aspiration and the onset of respiratory symptoms. Less frequent chronic exposure to relatively large quantities of talc may result in pulmonary fibrosis.

When inhaled, water-insoluble talc dries up the mucous membranes of the tracheo-bronchial tree. In fact, the mucous membrane of a 5-month-old baby girl observed during an emergency tracheostomy was described as '...a dry painted wall'. Drying of the epithelium leads to an impairment of ciliary function. Impaired ciliary function is particularly significant since the ciliary escalator would normally function as the primary mechanism for clearing the talc particulate matter from the airways.

In addition to drying of the mucous membrane, inhalation of additional talc can lead to complete obstruction of the small airways resulting in respiratory distress syndrome or death. The mortality in severe

cases of talc toxicity can be quite significant. Wagner and Hindi-Alexander reported an a series of 27 cases which resulted in 9 deaths. A lower, but nonetheless high mortality rate (20%) was reported previously by Brouillette and Weber.

The principal strategies reported for the treatment of accidental aspiration of talc in pediatric patients have been the use of (a) anti-inflammatory steroids and (b) bronchial lavage. Some authors question the efficacy of saline lavage, however, because of talc's aqueous insolubility and the inherent risks of the procedure.

The most useful means of treatment appears to be the administration of a glucocorticosteroid. Parenteral (i.m.) dexamethasone (2 mg) every 12 h for 3-4 days or prednisone 3-5 mg•kg⁻¹•d⁻¹ for the same duration have been used with good results. Intravenous fluids, antibiotics and bronchodilators have also been found to be useful adjuncts.

The incidence of accidental inhalation of talc by infants is difficult to determine from the literature. Table I shows the results of 3 studies between 1998 and 2010. From these data, it is clear that considerable variation exists in the reported frequency of calls. A reasonable estimation, as of the early 2000s, would probably put the frequency at approximately several thousand cases nationwide per year. It is not clear if there has been a decline in pediatric talc inhalation following these reports. However, in view of the questionable efficacy of talc and its potential for producing pulmonary toxicity, there are no compelling indications for the use of talc-based topical powder for infants. A more desirable alternative would be the substitution of appropriate creams and lotions.

Table 1

Incidence of accidental inhalation of talc

Location	Child age	Calls	Period of time	Reference
ORADEA	<5 yr	40	6 mth	7
BEIUS	-	50	1 yr	41
SALONTA	3 yr or<	65	3 mth	8

INTRAVENOUS

One form drug abuse involves the crushing, 'solubilizing', filtering, and intravenous injection of oral medication containing psychoactive agents. Talc is present in many of these drug tablets because of its utility in holding the components of the formulation together and preventing the tablets from sticking to punches during manufacture. If the filtration step is inadequately

carried out by the user, talc can be inadvertently administered by the addict.

The terminal pulmonary arterioles and capillaries serve as a sieve for most of the talc crystals. Since most of the crystalline particles are retained in the lungs, the majority of pathological lesions are limited to the lungs. The trapped talc crystals produce pulmonary angiothrombosis, foreign body granulomas and pulmonary fibrosis. If the granulomas develop in the arteries, vascular endothelial proliferation and secondary thrombosis may lead to pulmonary hypertension and cor pulmonale. On the other hand, if the particles migrate into the adjacent interstitial tissue, the granulomas may develop in the interstitium, with resultant pulmonary interstitial fibrosis.

The early cellular response to foreign body microemboli has been studied in dogs. Investigators reported that the injection of suspended pentazocine tablets is associated with a rapid accumulation of neutrophils around intravascular talc crystals. The accumulation of neutrophils is a response to neutrophil chemoattractant being released from endothelial cells. The nature of the chemoattractant is unknown, but does not appear to be leukotriene B₄ or platelet-activating factor but, rather, a group of chemoattractant lipids.

The first report clearly associates talc with the development of pulmonary granuloma formation following intravenous drug abuse of tablets, also described the development of pulmonary hypertension due to thrombosis of small pulmonary arteries, arterioles and capillaries. These investigators studied the effect of 'Blue Velvet' – a combination of trielennamine and paregoric. That talc was the offending agent was subsequently shown in an experimental study in rabbits. An up-to-date summary of drugs associated with intravenous-talc-induced pulmonary toxicity, is shown in Table II.

Table 2

Drugs associated with intravenous-talc-induced pulmonary toxicity

Drug	Reference
Amphetamine	34
Cocaine	42
Heroin	43
Hydromorphone	44
Meperidine	18
Methadone	45
Methylphenidate	46
Pentazocine	23
Phenmetrazine	34
Phenyltoloxamine	47
Propoxyphene	48
Propylhexedrine	21
Tripelennamine	33

An additional problem related to intravenous talc is an apparent tendency to predispose users to infections. Animal studies with closely related silica can mimic this increased susceptibility to infection and suggest inhibition of macrophage function as the mechanism.

CONCLUSIONS

In conclusion, any tablet containing filler such as talc, cellulose or cornstarch, when inappropriately administered parenterally, has potential to embolize in the lung. This is particularly true for larger particles in the 10-17 μm range. The long-term consequences of the intravenous ingestion of large quantities of talc (approximately 20 000 tablets) are severe. In a follow-up study of 6 discontinued drug users, covering at least 10 years, all developed severe respiratory disability, with findings similar to emphysema, and 3 died from their disease. Successful management of drug-induced talc granulomatosis has been reported following the administration of prednisone, 60 mg daily.

Talc-induced pulmonary hypertension can potentially be a complicating factor in diagnosis. For example, a patient initially diagnosed as having a primary or idiopathic pulmonary hypertension was subsequently found to have pulmonary talc granulomatosis. Talc granulomatosis has also been reported to mimic the laboratory findings of pulmonary sarcoidosis and should be considered in the differential diagnosis of pulmonary disease.

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