Sudden Infant Death Syndrome: a possible primary cause

BA RICHARDSON*
Penarth Research International Limited, PO Box 142, St Peter Port, Guernsey, Channel Islands, GY1 3HT

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Summary: The hypothesis that poisoning by phosphines, arsines and stibines might be the primary cause of sudden infant death syndrome (SIDS) was investigated. Most mattress materials contain phosphorus or antimony compounds as fire retardant additives. Mattress materials in areas affected by the warmth and perspiration of the sleeping infant were found to be naturally infected by the fungus Scopulariopsis brevicaulis which is thought to be capable of generating phosphines, arsines and stibines from materials containing phosphorus, arsenic or antimony compounds. These gases may cause anticholinesterase poisoning and cardiac failure in infants, but contributory factors include the prone sleeping Position and overwrapping. In England and Wales, the progressive increase in SIDS between 1951 and 1988 seems to be related to increasing use of phosphorus and antimony compounds as fire retardents in cot mattresses.

Zusammenfassung: Untersuchung zur Hypothese, dass Vergiftung durch Phosphine, Arsine und Stibine möglicherweise Hauptursachen des plötzlichen Kindstodes (SIDS) sind. Die meisten Matratzen-Materialien enthalten Phosphor oder Antimon in Form von feuerhemmenden Additiven. Untersuchungen ergaben, dass das Matratzen-Material, bedingt durch Körperwärme und Schweissaussonderungen des schlafenden Kindes, mit dem Pilz Scopulariopsis brevicaulis infiziert ist von dem man annimmt, dass er Phosphine, Arsine und Stibine generieren kann aus phosphor-, arsen- oder antimonhaltigem Material. Diese Gase können eine Anticholinesterase-Vergiftung und ein Herzversagen des Kindes hervorrufen, wobei als weitere Faktoren das Schlafen in der Bauchlage oder übermässiges Zugedecktsein nicht ausgeschlossen werden können. Es scheint, dass die Zunahme an SIDS-Fällen in England und Wales im Zeitraum 1951-1988 in Verbindung gebracht werden kann mit der zunehmenden Verwendung von feuerhemmenden, phosphor- und antimonhaltigen Materialien bei Kindermatratzen.

Key Words: Pathology/medicine; SIDS; Fire retardents; Phosphorus; Arsenic; Antimony

* Honorary Rescarch Fellow, King Alfred's College, Winchester.

Introduction

A routine investigation into the deterioration of heavy reinforced plasticized polyvinyl chloride (PVC) fabric in 1988 disclosed that the damage was caused by fungal deterioration of the plasticizer, despite the presence of the preservative biocide 10,10'-oxybisphenoxyarsine (OBPA). It is well known that fungal activity in the presence of arsenic compounds can result in the generation of arsines (arsenic trihydride and related alkyl compounds), although it was expected that this effect would be prevented by the fungicidal activity of OBPA. This observation prompted the hypothesis that generation of these toxic gases from PVC cot mattress coverings might be the cause of sudden infant death syndrome (SIDS), particularly as it had been discovered about a century ago that mysterious illnesses in adults and deaths in infants were caused by generation of arsines through biodeterioration of wallpaper decorated with arsenical pigments such as Paris green, or secured with paste containing white arsenic (arsenious oxide) [1-8].

The fungus responsible for wallpaper deterioration had been identified as Scopulariopsis brevicaulis, and it was suspected that this same fungus might be involved in a cot mattress situation as it is commonly found in the domestic environment generating ammonia from nitrogen compounds such as proteins in meat, cheese, butter, damp leather and wool [9, 10].

Preliminary experiments

Small samples from new PVC cot mattress coverings, swabbed with spirit to minimize contamination, were placed on Petri dish malt agar plates inoculated with S brevicaulis. Growth spread from the point of inoculation in the normal beige hyphal form associated with this fungus but then spread rapidly round the edges of the PVC samples. The fungus did not spread over the PVC surface but it was observed that edges of the samples were distorted and that the fungal growth altered around the samples to a buff slime or crinkled form. Pieces of the affected PVC were stained in picro-aniline blue which is selectively absorbed by fungal tissue. Only the distorted edges retained stain, indicating that they had been invaded by the fungus, although few strands or structural details were visible because of the masking effect of the PVC matrix.

When growth was well developed, small pieces of mercuric chloride paper were introduced, supported by the edges of the dishes. This paper develops a yellow or orange coloration in the presence of reducing gases of arsenic such as arsines, but no color change was observed during these initial experiments; subsequent analysis of the PVC by solvent extraction and atomic absorption spectroscopy confirmed that organic arsenic compounds such as OBPA were not present. However, it was observed that technicians sometimes suffered headache, an early Symptom of arsine poisoning, when attending to the incubator containing these samples. As it is well known that S brevicaulis is able to convert nitrogen and arsenic compounds into the trihydride, ammonia and arsine, and related alkyl compounds, and as Group V/Vb of the periodic table includes in sequence nitrogen, phosphorus, arsenic and antimony, it would be surprising if phosphines and perhaps stibines were not also similarly generated; their formation does not seem to have been previously reported, although it has been suspected [11]. Phosphines and stibines similarly cause headaches and they also complex with mercury but form white compounds so that they cannot be detected in this way.

Silver nitrate paper darkens through the formation of reduced silver when exposed to these reducing gases but, before darkening, phosphines produce a yellow color, and arsines and stibines produce a pinkish brown color. The experiments were therefore repeated using both silver nitrate and mercuric bromide papers; mercuric chloride or bromide papers can be used but bromide is normally available from laboratory chemical suppliers. All new PVC cot mattress coverings produced a strong pinkish brown color with the silver but no color with mercury, indicating stibines, and subsequent analysis of the fabrics identified the source as antimony trioxide which is used in PVC as a fire retardent. In some cases, an additional yellow coloration with silver could be detected, indicating phosphines from the phosphate plasticizers that are often used when fire retardent properties are required.

S brevicaulis is described as protein tolerant and is usually found on protein substrates, but experiments in which nitrogen, phosphorus, arsenic and antimony compounds were scattered on malt agar plates indicated that growth is encouraged by the presence of any of these compounds, the presence of phosphorus causing the S brevicaulis to develop a distinct pink or red coloration instead of the normal lighter beige. Filter papers treated with the arsenical biocide OBPA at a series of concentrations encouraged growth until a threshold was reached at which the fungicidal properties began to dominate and suppress growth.

Samples of PVC cot mattress coverings from SIDS incidents were placed on Petri dish malt agar plates. Various domestic spoilage organisms developed but, in all cases where the samples were taken from areas affected by warmth and perspiration, a rim of buff coloured slime developed around the samples. This was characteristic of the slime form that had been observed in the original experiments involving a pure culture of S brevicaulis. The fungal growth seemed reluctant to spread far from the samples, but it was found that it was more active on plates prepared from malt with added nitrogen compounds, the most convenient medium being 5% malt and 5% soya flour agar. This medium was therefore used for all subsequent experiments on naturally infected materials, as it encouraged S brevicaulis to grow away from the samples so that its presence could be clearly identified. It was also recognized that the color changes on the silver and mercury papers were quantitative and depended on gas concentration and time of exposure, so that sensitivity could be improved by reducing the size of the test papers. There was often interference with color formation at the edges of the Petri dishes, presumably through external contamination, but this problem was avoided in later experiments by supporting the test papers on bent wire paper Clips on top of the agar plates.

Investigations on mattresses from SIDS incidents

Initially 50 mattresses from 45 SIDS incidents were tested, between March and September 1989, by placing small samples on malt/soya Petri dish plates and identifying generated gases using small strips of silver nitrate and mercuric bromide papers. Two mattresses were involved in five incidents. The mattresses included one cotton-covered, 26 PVC-covered, 15 PVC-covered with exposed foam at one or both ends, and 8 exposed foam alone; exposed foam mattresses, sometimes described as "safety" or

"vented" mattresses, are usually covered by cotton or polyester open weave fabric or net. There were 25 small mattresses from carrycots or moses baskets and 25 larger mattresses from drop-side cots; it is not known whether this distribution is normal or whether it indicates that a particular size or type of cot is more likely to be involved. All the mattresses were found to he infected by the fungus S brevicaulis, and all generated phosphines, arsines or stibines or mixtures of these gases, depending on their composition, from the area affected by the warmth and perspiration of the sleeping infants.

Although most of the mattresses had been used for previous infants, five had been purchased for use by the infant that had died. Two of these mattresses were PVC with exposed foam. The PVC coverings were brittle and pink stained, and generated phosphines from phosphate plasticizers. The exposed foams were also pink stained but no gases were detected. Another mattress was exposed foam which was pink stained and generated phosphine from a phosphate fire retardent component. These observations suggest that deterioration and gas generation develops more rapidly in mattress materials containing phosphates, and that pink staining, often in the shape of the sleeping infant, is always associated with the presence of phosphates and the generation of phosphines. Two infants died at less than one month old, both of them sleeping for the first time on mattresses in current use by older children. A strong arsine reaction on the mercury paper was only seen with one sample in this group; a PVC-covered mattress which had been issued by the British Army to a service family and which contained OBPA as a preservative. However, faint arsenic reactions were seen with many samples, apparently associated with arsenic impurities in the antimony trioxide used as a fire retardent in PVC. Bed coverings were also sometimes examined. Cotton sheets covering the mattresses were always saturated with perspiration if examined promptly, and gas generation was detected in three cots which were examined shortly after death and which were still warm.

Further investigations

More than 100 further cot mattresses were examined between September 1989 and July 1991, both from SIDS incidents and from normal situations not associated with deaths. In all cases the results were the same; the area affected by the warmth and perspiration of the sleeping infant was naturally infected by S brevicaulis, and phosphines, arsines or stibines, or mixtures of these gases, were detected, depending on the composition of the mattress materials. The detection method using silver and mercury papers is very sensitive to the trihydrides, the alkyl compounds giving fainter colorations. At incubation temperatures of about 22 ºC an antimony reaction indicated that only the trihydride, stibine, was present, as the alkyl compounds are not volatile at that temperature. Similarly, arsenic and phosphorus reactions indicated that the trihydrides phosphine and arsine were most likely to be present, although theoretically the methyldihydride compounds might also be detected. At normal cot mattress temperatures of about 37 ºC, the methyldihydride compound of antimony and the dimethylhydride and ethyldihydride compounds of phosphorus and arsenic are volatile. Doubts over the identity of the generated gases were prompted by reports that only alkyl compounds of arsenic were generated by biodeterioration, although it has not been actually established that the trihydride is not also generated [12-14]. The doubts over the identity of the detected gases cannot be easily resolved as it is difficult to generate sufficient gas for identification by, for instance, mass spectroscopy. However, the distinction between trihydrides and the alkyl compounds is actually irrelevant as all the compounds are toxic with similar poisoning action, and the rate of generation is likely to be a more significant factor.

The rate of gas generation from PVC samples was investigated in relation to temperature. Petri dishes containing samples from cot mattresses with well established growth were placed in a desiccator in a water bath and temperatures were varied between 18 and 44 ºC, allowing at least an hour for stabilization between each temperature change. Following stabilization, the desiccator was flushed with air, a test paper was introduced, and the desiccator was sealed. The rate of gas generation was then assessed by the rate of development of colour change in the test paper. A special sensitive test paper was used for this purpose, prepared by treating one end of wide range pH paper with mercuric chloride. The absorption of phosphines, arsines and stibines produced hydrochloric acid and an acid reaction, and the untreated part of the paper gave an alkaline reaction if there was any interference from ammonia generation. No ammonia was detected. Hyperthermia causes an increase in mattress temperature from 37º to about 42 ºC, and this experiment indicated an increase in gas generation of 10 to 20 times for this limited temperature change.

The finding that all cot mattresses were apparently infected by S brevicaulis and generating these toxic gases suggests that all infants are equally at risk, yet most survive; the SIDS rate in England and Wales in 1986-88 was about 2.3 per 1000 births. However, the temperature dependence suggests a greatly increased risk in infants affected by hyperthermia through a high environmental temperature, overwrapping or fever. Overwrapping also tends to increase the risk by

trapping the generated gases. Ammonia, phosphine, arsine and stibine have densities relative to air of 0.66, 1.17, 2.68 and 4.29 respectively, and the alkyl compounds are even denser. S brevicaulis generates all these gases in the cot environment if suitable compounds of nitrogen, phosphorus, arsenic and antimony are present. Mothers are usually aware of ammonia generation as the pungent odour and low density mean that it is detected above the cot but this also means that ammonia disperses readily, whereas phosphines, arsines and stibines are denser than air and odourless, accumulating on top of the mattress. The risk of poisoning by these gases is therefore greatly increased in infants sleeping in the prone or face down position, particularly if they are also well wrapped so that the gases are prevented from dispersing, and hyperthermia increases the rate of gas generation. It is well known that the prone sleeping position and overwrapping are both associated with an increased SIDS risk, and a current campaign by the Department of Health for England and Wales aims to reduce the SIDS risk by avoiding these conditions [15, 16].

Blood samples from three infants who had died on mattresses which were infected by S brevicaulis and apparently generating only stibine were analysed by Dr N Ward of the Trace Element Unit, University of Surrey. The antimony levels determined by inductively coupled plasma mass spectrometry (ICP-MS) using $^{121}Sb^{+}$ with a sensitivity of about 0.05 ng/ml were 2.8, 4.8 and 1.9 ng/ml, compared with normal ambient levels of 0.7 to 3.0 ng/ml in adults but less than 0.85 ng/ml in infants [17, 18]. These results suggest that the blood antimony level was increased by about 2.0 ng/ml by stibine poisoning, although the normal maximum level of 0.85 ng/ml in infants probably includes some contribution from mattress stibine in non-fatal situations. The known comparative toxicities of arsine and phosphine would suggest that poisoning might similarly increase arsenic and phosphorus levels in the blood by about 1.0 and 6.0 ng/ml respectively, but such increases would be undetectable with normal arsenic levels of 2.0 to 5.0 ng/ml and much higher phosphorus levels. These calculations suggest that lethal doses of phosphine, arsine and stibine in SIDS might be 60, 10 and 20 ng/ml body weights respectively. Mixtures of gases are probably additive in effect because of their identical mode of action. These gases are eliminated by excretion in urine and significant toxic effects can only develop when the rate of gas absorption exceeds the rate of elimination, such as when hyperthermia in an infant increases the rate of gas generation from the mattress materials. Antimony levels in urine can be used to monitor exposure in infants; arsenic may be checked in the same way, but normal phosphorus levels in urine are too high for this element to be monitored.

Toxicology of phosphines, arsines and stibines in relation to SIDS

Poisoning by phosphines, arsines and stibines is usually diagnosed in adults through erythrocyte haemolysis and Heinz body formation, but haemolysis develops only 6 to 24 hours after severe acute exposure and such symptoms are not normally associated with SIDS. If these gases are a cause of SIDS, death must result from some other action before erythrocyte haemolysis develops, either because infant erythrocytes are more resistant to haemolysis or because infants are more susceptible to some other poisoning action which occurs at very low doses. Suppression of respiration has been suggested as a poisoning action by these gases, although it is not known whether this results from a direct action on the chemoreceptors associated with respiratory control or through carbon dioxide neutralization in the blood through absorption onto the basic phosphonium, arsonium, and stibonium cations that are formed during poisoning. It has also been reported that phosphines, arsines and stibines cause depression of the central nervous system. This may indicate an anticholinesterase action which could also cause cardiac inhibition and vasodilation in infants through progressive accumulation of acetylcholine from the vagus nerve. This mechanism would be biochemically understandable and completely consistent with SIDS, as it would be undetectable except as hypoxia which is actually observed [14, 19-21]. It would also explain other unusual SIDS observations such as death a few minutes after Lifting the infant from the cot. Cardiac failure through excessive acetylcholine caused by vagus nerve dysfunction has been suggested as a cause of SIDS, although the effects and symptoms are identical with anticholinesterase poisoning [22, 23].

Discussion

There have always been unexpected and unexplained infant deaths, but deaths during sleep suddenly increased about 40 years ago, prompting Barrett [24] to propose that "unexpected deaths in sleeping quarters of apparently healthy infants" should be described as cot death, although the term crib death is preferred in North America. In 1969 Beckwith [25] proposed that "the sudden death of any infant or young child which is unexpected by history, and in which a thorough post-mortem examination fails to demonstrate an adequate cause of death" should be described as sudden infant death syndrome (SIDS). The adoption of this description as code 798.0 in the International Classification of Diseases resulted in publication of mortality statistics which demonstrated immediately that whilst SIDS is a serious problem in some areas such as western Europe and North America, it is not known in many other countries. There is some confusion over historical SIDS rates because of the diffi-

culty in diagnosing this condition, so that many SIDS cases were attributed in the past to other causes. It is clear, however, that the rates have increased steadily since the problem was first recognized about 40 years ago, reaching a peak in England and Wales in 1986-1988, and coinciding with the use by cot mattress manufacturers of highest loadings of fire retardents based on phosphorus and antimony. These high loadings were prompted by the introduction of the Furniture and Furnishings (Fire) (Safety) Regulations 1988 which do not actually apply to mattresses, although all filling materials, now mainly foam, must be fire resistant as they may be used in other furnishings subject to these regulations. Most manufacturers use coverings conforming with British Standard fire retardent requirements as a prudent precaution and because compliance with these requirements is a marketing aid.

All cot mattresses become naturally infected in use by micro-organisms, and as most cot mattresses contain phosphorus and/or antimony fire retardents, most infants are at risk from toxic gas generation. Whether an infant is unaffected or suffers irritability, illness or death depends on various contributory factors. The most important of these is sleeping in the prone position, which involves greatest exposure to these heavier-than air gases, and overwrapping which causes hyperthermia and inereased gas generation, as well as trapping the gas [15, 16, 26-28]. The importance of these factors is illustrated by the substantial reduction in SIDS rates that has been achieved by avoiding the prone sleeping position and overwrapping [15, 16].

Conclusions

The hypothesis that the primary cause of SIDS is inhalation of phosphines, arsines and stibines generated by biodeterioration of mattress materials containing phosphorus, arsenic and antimony compounds, is consistent with all the established features of SIDS. The progressive increase in SIDS rates over the last 40 years can be related to increasing use of phosphorus, arsenic and antimony compounds in mattress materials. SIDS is not recognized in countries where these compounds are not used, such as Japan, where infant futons are manufactured from cotton treated with boron preservatives and fire retardents.

Whilst the SIDS risk and death rate can be reduced by various precautions aimed at contributory factors such as the prone sleeping position, SIDS will only be eliminated in affected countries by avoiding the elements phosphorus, arsenic and antimony in mattress materials. Elimination of SIDS will not mean the total elimination of unexpected and unexplained infant deaths, but it will mean a return to the low rates that occurred in the British Isles before 1950 and which still occur today in countries such as Japan which are unaffected by SIDS.

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