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Adverse reactions to the non-drug constituents of nebuliser solutions

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Nebulisation has become a commonly used method for administering pharmacological agents used in the treatment of respiratory disorders. In particular it is widely used in the treatment of asthma and related inflammatory diseases of the airways, for this method allows high doses of drugs to be delivered to the lung despite the presence of airflow obstruction. Although the efficacy of this form of drug delivery in relation to bronchodilator and disease modifying agents was soon established, reports began to appear of non-drug related complications associated with its use (Connolly, 1982; Edmondson *et al.*, 1966; Jolombe, 1982; Koepke *et al.*, 1983; Kuhn *et al.*, 1982; Mertz *et al.*, 1967; Morris, 1973; Reinarz *et al.*, 1965; Reisman, 1970; Sanders *et al.*, 1970; Trautlein *et al.*, 1976; Twarog & Leung, 1982). Despite efforts to overcome these problems, there have been a number of recent reports demonstrating significant side effects with the currently available formulations of nebuliser solutions, particularly paradoxical bronchoconstriction (Barnes *et al.*, 1987; Beasley *et al.*, 1987; Clark, 1986; Jones *et al.*, 1985; Mann *et al.*, 1984; O'Callaghan *et al.*, 1986; Prendiville *et al.*, 1987). In this article the problems associated with the formulation and administration of nebuliser solutions are reviewed, and some suggestions made regarding their use.

Osmolality

During the past 10 years, reports from several laboratories have shown that in asthmatic subjects inhalation of nebulised distilled water provokes bronchoconstriction (Allegra & Bianco, 1980; Anderson *et al.*, 1983; Ellwood *et al.*, 1982; Eschenbacher *et al.*, 1984; Lilker & Jauregi, 1981; Sheppard *et al.*, 1983). The bronchoconstriction relates to the low osmolality of the water, for addition of dextrose or a variety of chemically unrelated solutes to render the solution isosmolar prevents the adverse airways response. In addition to being implicated in the pathogenesis of exercise-induced asthma, the clinical importance of osmolality in relation to bronchoconstriction was demonstrated when ipratropium bromide nebuliser solution first became available. When administered to asthmatic subjects as a hypotonic solution of 250 $\mu g\ ml^{-1}$, it frequently caused initial paradoxical bronchoconstriction. Falls in forced expiratory volume in 1 s (FEV_1) of > 50% occurred in some subjects whose airways exhibited greatly enhanced non-specific responsiveness (Mann *et al.*, 1984). In contrast this marked effect was not observed when the ipratropium bromide solution was rendered isotonic.

Hyperosmolar solutions have also been shown to produce bronchoconstriction in asthmatic subjects (Elwood *et al.*, 1982; Eschenbacher *et al.*, 1984; Smith & Anderson, 1986). In addition, it has been demonstrated that, with evaporation of water from nebulised droplets, the solutions within the nebuliser reservoir become progressively more hyperosmolar during nebulisation (O'Callaghan *et al.*, 1986). By this mechanism the osmolality of an isotonic solution approaches 350 mosmol l^{-1} after 5 min of aerosolisation by jet nebuliser (O'Callaghan *et al.*, 1986).

Both hypotonic and hypertonic nebuliser solutions produce bronchoconstriction through a combination of mast cell and reflex-mediated mechanisms (Anderson *et al.*, 1983; Ellwood *et al.*, 1982; Eschenbacher *et al.*, 1984; Lilker & Jauregi, 1981; Sheppard *et al.*, 1983). Recently the range of osmolality required to provoke the adverse airways response has been determined (Ellwood *et al.*, 1982). In this study, the degree of airflow obstruction occurring in asthmatic

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subjects after inhalation of aerosol solutions of between 0 and 1665 mosmol for a period of 2 min was assessed by measurement of the FEV_1. No significant change in FEV_1 was observed after inhalation of solutions with an osmolality between 150–549 mosmol. To achieve a fall in FEV_1 of 20% from baseline, it was necessary to administer either distilled water on the one hand or saline with an osmolality of > 1089 mosmol on the other. These observations suggest that if solutions are formulated as isotonic, they will not cause an appreciable adverse reaction in the airways, even if they become more hypertonic during nebulisation. Thus if it is thought appropriate to dilute the nebuliser solution (or increase its volume to improve nebuliser efficiency) it is important to supply patients with isotonic saline for this purpose. A recent community-based study has shown that only a minority of patients use isotonic solutions to dilute their bronchodilator nebuliser solutions, the remainder using water or propylene glycol (Jones *et al.*, 1985).

Acidity

Another variable predisposing to paradoxical bronchoconstriction with inhaled solutions is their level of acidity. When inhaled by asthmatic subjects, acidic aerosols cause bronchoconstriction in direct proportion to the hydrogen ion concentration (Fine *et al.*, 1987; Koenig *et al.*, 1983; Utell *et al.*, 1983). Although the method of inhalation, the particle size, specific chemical composition of the acid aerosol and the titratable acidity are all important factors contributing to the airways response, marked increases in airways resistance are likely to occur only when the pH of the solution is 2 or less (Fine *et al.*, 1987; Utell *et al.*, 1983). However, solutions with a lesser degree of acidity can also have an important effect on the airways. For example, the airways response to inhaled histamine may be doubled if the pH of the solution falls below 5.0 (Cockcroft & Bercheid, 1982). Since many drug solutions prepared for nebulisation have been acidified to a pH of 3–4 to extend the life of the active drug constituent, occasional adverse responses resulting from hydrogen ion interactions with inflamed and hyperresponsive airways are to be anticipated.

Preservatives

In addition to containing the active pharmacological agent, the majority of solutions used in nebulisers contain chemical additives with antimicrobial properties. Unfortunately, these additives can cause bronchoconstriction when inhaled by asthmatic subjects in concentrations equivalent to those present in the nebuliser solutions. This problem was initially recognised in patients with asthma following reports that inhaled isoprenaline solution containing sodium metabisulphite caused paradoxical bronchospasm (Reisman, 1970; Trautlein *et al.*, 1976). This adverse response has subsequently been shown to be the consequence of sulphur dioxide (SO_2) released from solutions containing sulphites. Sulphur dioxide levels ranging from between 0.1–6.0 parts per million (ppm) have been reported in nebuliser solutions commercially available for bronchodilator use (Koepke *et al.*, 1983; Schwartz & Chester, 1984; Witek & Schachter, 1984). Sensitive asthmatics may experience bronchospasm while exercising when inhaling as little as 0.1 ppm SO_2 (Sheppard *et al.*, 1981), and even non-asthmatics may develop bronchospasm at a level of 6 ppm (Sheppard *et al.*, 1980). Recently, Dixon *et al.* (1987) have shown that sodium metabisulphite solution is a potent bronchoconstrictor whose effects are inhibited by nedocromil sodium, a mast cell stabilising agent but not oxitropium bromide, a muscarinic cholinergic antagonist. This might suggest that SO_2 stimulates bronchoconstriction by augmenting mast cell mediator release and/or stimulating sensory irritant nerves in the bronchial mucosa. Thus the presence of sulphite preservatives in nebuliser solutions represents more than a theoretical risk to asthmatic patients, and it is a matter of concern that one of the commercially available preparations of a β_2-adrenoceptor agonist still contains sodium pirosulphite.

The preservative most commonly present in nebuliser solutions is benzalkonium chloride, a mixture of benzyldimethylalkylammonium chlorides. This agent is incorporated for its bacteriocidal properties and is present in commercially available salbutamol, beclomethasone diproprionate and ipratropium bromide nebuliser solutions. Following reports that paradoxical bronchoconstriction may occur in asthmatic subjects following inhalation of these solutions (Beasley *et al.*, 1987), the airways effects of this agent have been investigated. When inhaled by asthmatic subjects, benzalkonium chloride produced dose-related bronchoconstriction over a concentration range of 0.13–2.0 mg ml^{-1} which persists for > 60 min. Recent investigations indicate a combined effect of benzalkonium chloride in augmenting mast cell mediator release, and stimulating cholinergic and non-cholinergic nerves in the airways to produce bronchoconstriction (Miszkiel *et al.*, 1988a, b).

Fenoterol and ipratropium bromide nebuliser solutions also contain ethylenediamine tetraacetic

acid (EDTA) which is a bronchoconstrictor agonist but less potent than benzalkonium chloride on a mass basis (Beasley *et al.*, 1987). In addition to causing bronchoconstriction in dogs, this agonist also increases bronchial responsiveness to inhaled histamine (Downes & Hirshman, 1985), an effect that has been attributed to calcium chelation and not to either the acidity or osmolality of the solution (Downes & Hirshman, 1983).

In the case of ipratropium bromide removal of the preservatives enhanced the speed of onset and magnitude of bronchodilatation (Rafferty *et al.*, 1988). Thus although anticholinergic or β_2-adrenoceptor drugs in the nebulised solution may antagonise any tendency for preservatives to provoke bronchoconstriction, their removal from nebuliser solutions or replacement by a non-constrictor agent will remove the risk of an unpleasant and potentially dangerous effect and possibly enhance the efficacy of the active drug.

Bacterial contamination

Nebulisers used in the treatment of airways diseases are designed to produce aerosol particles of a size that will reach the most peripheral airways ($< 5\ \mu$) and therefore bypass the protective muco-ciliary and cough reflex mechanisms operating in the upper airways. Thus, the use of equipment or solutions that are contaminated with microorganisms represents a potentially effective method of delivering pathogens to the lung and maintaining or spreading infections. This was originally recognised when outbreaks of pulmonary infection, often with unusual bacteria, were traced to bacterial contamination of nebuliser solutions used in hospitals (Edmondson *et al.*, 1966; Mertz *et al.*, 1967; Morris, 1973; Reinarz *et al.*, 1965; Sanders *et al.*, 1970). More recently, a high incidence of bacterial contamination of nebuliser units and solutions has also been identified in domiciliary practice (Barnes *et al.*, 1987; Jones *et al.*, 1985). In a study of 52 patients requiring treatment with domiciliary nebulised salbutamol, 61% of the nebuliser solutions and/or aerosols were found to be contaminated (Jones *et al.*, 1985). In the majority of cases, contamination of the nebuliser reservoir and solution was the source of aerosol contamination, thereby confirming previous reports of nebuliser contamination in hospitals. In a subsequent community based study, an inverse relationship has been shown between the frequency of bacterial contamination and the presence of antibacterial agents in the drug solutions (Barnes *et al.*, 1987). This study also made the observation that bacterial contamination was less likely to occur if the nebuliser solutions were administered in unit dose vials prepared under sterile conditions.

An effective method for cleansing nebuliser equipment can be obtained from recommended guidelines (American Thoracic Society, 1968), and from some of the studies in which the problems of bacterial contamination have been identified (Jones *et al.*, 1985; Morris, 1973). Nebuliser units can be used for at least 2 weeks without the risk of bacterial contamination, which suggests that the routine daily replacement of units is unnecessary. Nebuliser units should, however, be washed regularly and dried after use. The frequent use of chemical agents such as benzalkonium chloride, ethylene oxide, glutaraldehyde and acetic acid for cleaning the nebuliser equipment has also been recommended but care must be taken to rinse the units in water prior to use.

Conclusions

On the basis of experimental work we suggest that wherever possible nebuliser solutions should be formulated as isotonic solutions, with a pH > 5.0. If it is considered necessary to incorporate bacteriocidal agents in the solutions due to the risk of bacterial contamination, then the commonly used preservative agents which are liable to cause bronchoconstriction, should be replaced by safer substitutes (which remain to be identified). Ideally, nebuliser solutions should be prepared under sterile conditions in unit dose vials and in volumes and concentrations which should not require modification by the user. It is also recommended that physical and chemical cleansing of the nebuliser units should be undertaken by the user on a regular basis and that under no circumstances should the equipment be shared by patients unless scrupulous attention is paid to cleaning the units. With implementation of some or all of these guidelines the safety and possibly the efficacy of nebuliser therapy for airways diseases should improve.

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