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Ribavirin treatment for juvenile respiratory papillomatosis

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Abstract

Juvenile respiratory papillomatosis involving the tracheo-bronchial tree imposes a significant management problem and is sometimes life threatening. The mainstay of treatment is repeated vapourization with a CO_2 laser. To date, adjunctive medical treatments have been of limited value. A tracheostomized child with extensive laryngo-tracheo-bronchial papillomatosis who has required bronchoscopic lasering at two-weekly intervals for three years was treated with ribavirin, a broad spectrum anti-viral agent. The drug was administered in nebulized form using a small particle aerosol generator (S.P.A.G.) to the lower respiratory tract (6 gm/150 ml over nine hours) on three consecutive nights every two weeks over seven weeks and also administered orally (15 mg/kg/day). Endoscopic assessments were made every two weeks. At 14 days the papillomata were regressing and far less lasering was required. No further lasering was required up to 56 days. One month after stopping the ribavirin, however, a few sessile papillomata in the tracheo-bronchial tree had recurred and were treated with the laser. No adverse reactions were encountered. During the treatment period there was a significant reduction in the frequency of therapeutic endoscopies. This promising response requires further evaluation to define the role of ribavirin in the treatment of juvenile respiratory papillomatosis.

Key words: Papilloma; Laryngeal neoplasms; Tracheal neoplasms; Bronchial neoplasms; Ribavirin.

Introduction

The mainstay of treatment for juvenile respiratory papillomatosis is repeated vapourization with a CO_2 laser. The aetiology is viral and human papilloma virus (HPV) types 6 and 11 have been associated with the condition (Quiney *et al.*, 1989; Metcalfe *et al.*, 1989; Kashima *et al.*, 1991). Surgical treatments are not usually curative and carry some risk of laryngeal or lower airway scarring. The multifocal nature of the disease would lend itself well to an effective medical treatment. Patients with respiratory papillomatosis may demonstrate reduced immunocompetency (Perrick *et al.*, 1990) and both immunomodulating agents and anti-viral drugs have been employed. The use of interferon has been extensively explored (Lundquist *et al.*, 1984; Benjamin *et al.*, 1988; Leventhal *et al.*, 1988; Mattot *et al.*, 1990). After initial enthusiasm with its use, substantial lasting remissions have not been seen at Great Ormond Street. A multi-centre trial which included these patients showed that after the first six months of treatment the benefits of interferon were no longer significant (Healey *et al.*, 1988). A correlation between the dose of interferon and the response has been shown (Mullooly *et al.*, 1988), but this drug is not without adverse effects (Crockett *et al.*, 1987). Numerous other medical treatments have been given including inosane prenobex (Immunovir) (Patel *et al.*, 1987), adenine arabinoside (Hendrickse *et al.*, 1985), lysozyme chlorhydrate (Altmar, 1990), and acyclovir (Aguado *et al*, 1991; Morrison and Evans, 1992). While some of these may appear to have had a beneficial adjuvant effect, none has been established as having a major role in the treatment of juvenile respiratory papillomatosis.

At The Hospital for Sick Children, Great Ormond Street, a number of young children with aggressive and life threatening respiratory papillomatosis are treated by regular CO_2 laser vapourization. In a search for a new and effective medical treatment ribavirin (Virizid) was used as a compassionate trial in one patient.

Ribavirin (1-beta-D-ribofuranosyl-1, 2, 4-triazole-3 carboxamide), first synthesized in 1970 and whose parent compound was a product of *Streptomyces*, has broad antiviral activity (Sidwell *et al.*, 1972). Activity has been demonstrated against a range of both RNA and DNA viruses including influenza A and B, parainfluenza 1 and 3, lassa fever and respiratory syncytial virus (RSV) (Fernandez *et al.*, 1986). It is a highly soluble nucleoside, exerting its antiviral action after phosphorylation to mono-, di- and triphosphate nucleotide structures. It appears to have multiple antiviral mechanisms and its primary action leads to intracellular virustasis (Eriksson *et al.*, 1977; Goswami *et al.*, 1979; Smith, 1980; Patterson and Fernandez, 1990). It has also been demonstrated to inhibit human immunodeficiency virus reverse transcriptase (Fernandez and Patterson, 1990). Extensive clinical experience of the drug has been obtained in the treatment of infants and children with RSV infections where it is used in high risk patients, on and off ventilators, with conditions such as cyanotic congenital heart disease and bronchopulmonary dysplasia, and where there is immunosuppression (Hall *et al.*, 1985; McIntosh, 1987; Rodriguez and Parrott, 1987; Englund *et al.*, 1990). In the main, this drug has been extremely well tolerated especially by aerosol administration. No previous report has been found of the use of ribavirin in respiratory papillomatosis.

Ribavirin is available for administration via aerosol

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inhalation, by injection or orally. The pharmacokinetics has been studied by Fernandez *et al.* (1986) using radioimmunoassay. Following oral administration (1,000 mg/day) plasma concentrations are low (mean 3.1 microMol. at 2.5 hours) but an accumulation does occur in red blood cells and after continued oral administration a modest fall in haemoglobin is often seen (Schulman, 1984). Intravenous ribavirin (1,000 mg 6 hourly) gives considerably higher plasma concentrations (mean 94 microMol. after 4 days), and systemic levels of the drug are very low following aerosol administration to the lower respiratory tract (1.1 microMol. after 5 hours treatment per day). Peak local concentrations however are very high with tracheal secretion ribavirin concentrations of 1,000–7,000 microMol.

The concept of using aerosol administration directly to the respiratory papillomata, thereby providing very high local concentrations of ribavirin without significant systemic effect, is the natural approach and was therefore adopted in this trial. Initially, however, treatment was augmented with the administration of oral ribavirin because of the extensive laryngeal disease which would not receive the aerosol drug since delivery was through the tracheostomy in this case.

Ribavirin for aerosol administration and the small particle aerosol generator (S.P.A.G.) is available in the U.K. from Britannia Pharmaceuticals Limited under the trade name 'Virazid'. Ribavirin is available in the oral form from Antigen Pharmaceuticals Limited, Eire, on a named patient basis. The intravenous preparation is available from I.C.N. Pharmaceuticals, Buckinghamshire.

Case Report

A 3½-year-old girl (K.W.) had life threatening laryngo-tracheo-bronchial papillomatosis. She was born premature at 23 weeks gestation (birth weight 690 gm). She required ventilatory support for her first 5 months with numerous failed extubations because of stridor and at this stage a tracheostomy was performed. Laryngeal papillomatosis was first diagnosed and confirmed histologically when she was 3 months old. By 6 months of age papillomata had spread to the trachea and bronchi. She required admission for laryngoscopy and bronchoscopic diathermy (until the age of 10 months) or bronchoscopic laser treatment (from the age of 10 months) every two to three weeks to control her disease since the tracheostomy was performed. She underwent over 80 such procedures in her first 3 years of life. She was also treated with adjunctive interferon (3 MegaU i.m. injection three times per week) for 18 months, from the age of one year, with the additional treatment 2 or 3 MU injections directly into the laryngeal papillomata on nine occasions between 16 and 19 months of age. The larynx has been obliterated by papillomata since the tracheostomy was fashioned and she received CO_2 laser treatment only to the extensive tracheal and right and left main bronchial papillomata. She has suffered from recurrent *Haemophilus influenza* and *Staphlococcus aureus* chest infections and had two episodes of respiratory arrest requiring emergency resuscitation within the 6 months immediately prior to starting ribavirin. A course of oral acyclovir (100 mg five times per day) was given for 3 months without benefit from the age of 2½ years. From 2 years of age she has had some degree of reversible airways obstruction responding with limited success to nebulized salbutamol and cromoglycate. Her weight has remained just below the third percentile all her life.

In spring 1992, when 3 years and 5 months old, she was commenced on ribavirin by both the oral and the inhaled route. The oral dose was 100 mg b.d. (based upon 15 mg/kg/day) and the aerosol dosage was 6 gm ribavirin dissolved in a final volume of 150 ml water (concentration, 40 mg/ml) delivered using a small particle aerosol generator (S.P.A.G.) through her tracheostomy over nine hours overnight. The circuit was open at the tracheostomy (Fig. 1), the aerosol being delivered at pressure of 26 psig at 12.5 l/min through a tracheostomy mask positioned over the tracheostomy. The room was well ventilated. This treatment was repeated on three consecutive nights every 14 days for 7 weeks. A total of 12 overnight aerosol administrations (3 nights × 4) were given. Full blood count, urea and electrolytes and liver function tests were monitored prior to starting treatment and every 14 days thereafter. Laryngoscopy and bronchoscopy under general anaesthesia was performed every two weeks as before with laser vapourization where required and video photography to help with subsequent objective assessment of response. In the two months prior to ribavirin treatment there had been a need for bronchoscopic lasering to the trachea and both right and left main bronchi every twoweeks for aggressive papillomatosis. On the first endoscopy, two weeks into her treatment there was already an improvement in the appearance of the disease but lasering was carried out. On the subsequent two endoscopies over the next four weeks, following continued ribavirin administration, there was a convincing further reduction in papillomatosis to such an extent that no lasering was required at all. On the next endoscopy three weeks later and 25 days after the last treatment of ribavirin some lasering was again required around the stoma. Throughout this time, however, the laryngeal disease remained very extensive, suggesting no significant response to the systemic oral ribavirin. Throughout the treatment the full blood count, urea and electrolytes and liver function tests remained within normal limits, with no drop in blood count or haemoglobin and no adverse effects noted. The dissolved aerosol ribavirin however was noted to crystallize out during administration leaving a deposit around the face mask and within the tracheostomy tube. Close observation was therefore required during administration

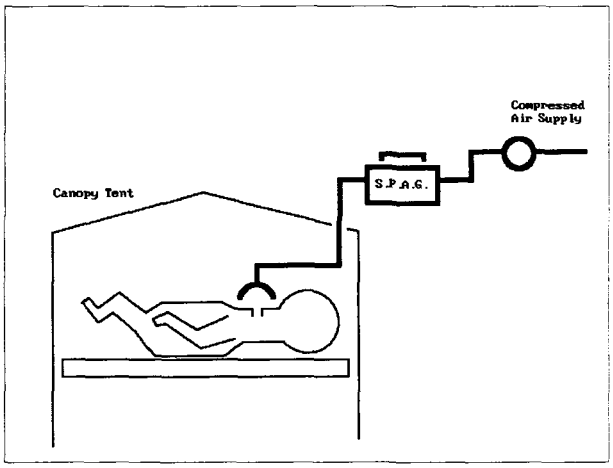

FIG. 1
Ribavirin aerosol administration via the tracheostomy.

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and occasional tracheal tube suction was applied to ensure there was no tube obstruction.

Subsequent scrutiny of video recordings of the trachea and bronchial tree and operative records confirmed a substantial reduction in the papillomata which were initially florid and tending to obstruct the main bronchi and subsequently showed regression to flat sessile non obstructive lesions despite only one episode of lasering early in the treatment period. This was a marked reduction in the aggression of the papillomata compared with their consistent behaviour over the previous year. Following withdrawal of ribavirin treatment regular endoscopies were continued with lasering as required and over the next three months the papillomatosis again became more aggressive with a tendency to occlude the airway both in the trachea and main bronchi.

Discussion

This investigation into the treatment of juvenile respiratory papillomatosis has involved the pilot trial of ribavirin to one child with severe disease of the lower respiratory tract. It is difficult to achieve a satisfactory controlled study for treatment of this condition. The mainstay of treatment is at present repeated CO_2 laser vapourization, and therefore any new medical treatment must be applied as an adjunct to this, making strict assessment of response to the drug difficult. By comparing the severity of the papillomata for a long period prior to commencing treatment, throughout administration and then after withdrawal of any new drug, the patient acts as her own control. It must be acknowledged that the fluctuant natural history of the condition means that small variations in the extent of disease may not be the result of any specific new treatment. Nevertheless, scrutiny of the results of ribavirin administration, in as objective a fashion as possible, utilizing endoscopic videotape comparisons suggests a startling response to this agent. This patient had consistently required substantial tracheobronchial lasering every two weeks for much of her life even with long term adjunctive interferon. Shortly after ribavirin was given, however, the papillomata became sessile and no lasering was required at all over eight weeks. Following withdrawal of treatment, disease resurgence was observed once again. This strongly suggests a genuine beneficial effect of ribavirin on juvenile papillomatosis.

No toxicity or adverse effects were evident throughout or after this oral and aerosol inhaled regimen of ribavirin administration. Blood count was closely monitored since ribavirin triphosphate is known to accumulate in erythrocytes even following aerosol administration (Englund *et al.*, 1990) and anaemia has been reported following systemic administration (Schulman, 1984). There was no significant change detected however in any of the indices of a full blood count including red cell count, haemoglobin concentration, platelet count or white cell count during therapy. Similarly urea, electrolytes and liver function tests remained within the normal range. Progressive deposits of crystallized ribavirin were noted to precipitate out on the face mask supplying the drug and in the inside of the tracheostomy tube during administration. This did not cause any tube obstruction but clearly it is a potential hazard and close observations with suction to clear deposits as necessary is required with this form of administration. This phenomenon has been previously reported (Rodriguez and Parrott, 1987; Englund *et al.*, 1990) and Rodriguez and Parrott (1987) suggest greatly reducing the drying air supply of the S.P.A.G. to avoid this complication. Most other potential side effects are only seen in severely ill patients with underlying cardio-respiratory disease and as such a causal relationship has not been firmly established with ribavirin. They include aggravation of bronchospasm, pneumonia, pneumothorax (in ventilated patients), apnoea, ventilatory dependence, cardiac arrest, hypotension, digitalis toxicity, rash and conjunctivitis (Rodriguez and Parrott, 1987). One case of death has been reported in which an infant with RSV infection and a septal defect with patent ductus arteriosus suffered a dramatic decrease in oxygenation immediately following administration of inhaled ribavirin. It is postulated that ribavirin brought about an increase in pulmonary arterial pressure and an increased shunting of blood in this persistent fetal circulation (Cosgrove *et al.*, 1989).

Fetal malformations have been documented after oral administration of ribavirin to pregnant rodents and rabbits (Kilham and Ferm, 1977) and this has led to understandable concern about a possible risk of teratogenic effects on hospital personnel in contact with inhaled ribavirin (Guglielmo *et al.*, 1989; Bradley *et al.*, 1989; Gladu and Ecobichon, 1989). No skeletal malformations were observed however in baboons treated with the drug orally (Hillyard, 1980). When ribavirin is administered by aerosol with an open circuit, substantial amounts of it may escape into the air around the patient and both visitors and staff caring for the infant may be exposed to the drug, primarily by inhalation. Ribavirin has been detected in room air during its administration to patients via an oxygen tent. Urine and blood sampling from ten exposed personnel however detected ribavirin (0.44 micrograms/ml) in only one red blood cell specimen from one exposed nurse (Harrison *et al*, 1988). In another study (Rodriguez *et al.*, 1987), blood and urine were assayed for ribavirin in 19 nurses caring for children receiving ribavirin and none of the drug was detected in 30 samples obtained over three days of exposure. There have been no reported cases of developmental toxicities associated with ribavirin use in humans. To minimize risks to personnel, however, a simple containment system consisting of a canopy tent with mist and suction using a standard wall suction unit, has been recommended by Torres *et al.* (1991) and appears effective. They also recommended discontinuing the administration of ribavirin for five minutes while continuing suction to rapidly reduce ambient ribavirin prior to attending the patient where possible. Gladu and Ecobichon (1989) also suggest the use of a tent and point out that added protection could be provided by the use of surgical gloves and a respirator by attending personnel. The ribavirin exposure to personnel in their study fell well below their calculated estimates of a human safe exposure level of 1.2 mg/kg body weight. At The Childrens Hospital, Boston, USA, even more stringent precautions are taken (Fackler *et al.*, 1990). Given the possible potential risk of teratogenesis in humans it is clearly sensible for anyone who is known to be or likely to be pregnant to avoid caring for a patient being treated with ribavirin aerosol. In the case we report above the drug was administered via a tracheostomy mask within an oxygen tent in a well-ventilated side room. The patient did not cooperate fully

with the use of the tent zipped closed throughout administration and no suction or exhaust air ducting was employed. Any hospital prescribing ribavirin should adopt their own guidelines for its safe administration. On the available evidence, with sensible precautions, the risk to personnel appears very small indeed.

In conclusion, while the improvement seen in papillomatosis following ribavirin treatment to a single patient is not proof of the drug's efficacy, the apparent response was sufficiently encouraging to suggest the need for a trial, possibly in multiple centres, on a large number of patients with juvenile respiratory papillomatosis.

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