Tobramycin nebuliser solution

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Introduction

The regular daily administration of a nebulised antibiotic has been an established treatment since Hodson *et al* published their paper in 1981 comparing nebulised gentamicin and carbenicillin with placebo in a double blind cross-over trial in 20 adult patients (Hodson *et al*, 1981). Subsequent studies using various antibiotics have shown improved lung function, a slower decline in respiratory function, decreased hospital admission rates, better clinical scores, and better weight profile in patients who receive daily nebulised antibiotic treatment.

The intermittent administration of nebulised colistin or tobramycin in combination with either oral ciprofloxacin or intravenous antipseudomonal antibiotics have proved effective in the early eradication of new isolates of *Pseudomonas aeruginosa* (PA).

In this article we will review the evidence for the use of Tobramycin nebulised solution (TNS) in patients with cystic fibrosis.

What is Tobramycin nebulised solution (TNS)

Tobramycin is an aminoglycoside antibiotic which acts on susceptible bacteria by irreversibly binding to the 30S ribosomal subunit and inhibiting protein synthesis. Its spectrum of activity include coverage against most species of *E. coli, Klebsiella, Proteus, Pseudomonas, Salmonella, Enterobacter, Serratia, Shigella, Mycoplasma, and Staphylococcus*. It is highly active against both mucoid and non mucoid strains of PA (Govan, 2002).

Inhalation of 300 mg of Tobramycin is associated with significantly higher sputum concentrations than those achieved following intravenous administration of the usual therapeutic doses of Tobramycin, with bactericidal levels being reached which are well above MIC90 for PA.

Prior to the introduction of TNS, the standard intravenous formulation of Tobramycin had to be used for nebulisation. This has now been superseded by the introduction of TNS (TOBI®), a drug which has been specifically developed as a preservative free, formulation, which approximates the pH and osmolarity of the lung.

TNS is licensed for the long term management of chronic pulmonary infections caused by *P. aeruginosa* in patients with CF aged six years and older.

Evidence for the use of Tobramycin nebulised solution

In 1993, Ramsey *et al* reported their findings of a short term randomised multicentre crossover study evaluating the safety and efficacy of aerosolized TNS in patients with cystic fibrosis and PA infections (Ramsey *et al*, 1993). Each patient was randomized to receive either tobramycin (600 mg) for 28 days followed by placebo for two 28 day periods or placebo for 28 days followed by tobramycin for two 28 day periods. A total of 66 out of 71 patients completed the study. Active treatment was associated with a significant reduction in sputum PA density. The frequency of tobramycin resistance was similar during both placebo and tobramycin administration. Active treatment with tobramycin resulted in improvements in mean FEV_1, FVC and FEF25-75, which declined on discontinuation of therapy. While there was no difference between the two study groups in the frequency of exacerbations, more patients on placebo received antibiotic treatment (oral and parenteral) by the third month ($p=0.006$). The study found no association with the use of tobramycin and increased ototoxicity. Rather surprisingly, creatinine concentrations rose transiently by 50% in six and five patients during tobramycin and saline administration respectively. The administration of TNS was associated with 100 fold reduction in PA density in sputum. There was a trend towards a reduction in the peripheral blood neutrophil count.

More recently the results of two large multicentre, double blind, placebo controlled studies have been

published (*Ramsey et al, 1999*). A total of 520 patients were randomly assigned to receive either 300 mg of inhaled TNS (n=258) or placebo (n=262) twice daily for four weeks followed by four weeks without inhaled therapy. Each patient received a total of three cycles, with each cycle consisting of 28 days during which the drug was administered and 28 days during which it was not (total 24 week study period). The primary end point was FEV_1 and PA sputum density. The secondary points included hospitalisation and intravenous antibiotic therapy.

TNS was associated with a dramatic improvement in FEV_1 following the first two weeks of therapy and this remained elevated throughout the study period. At week 20, active treatment was associated with an average 10% and 8% increase in FEV_1 and FVC respectively as compared to 2% and 1% in the placebo group. Patients who were 13 to 17 years old had significantly greater increase in FEV_1 compared with individuals who were either younger or older. Treatment with TNS was also associated with improvement in quality of life scores.

The density of *P. aeruginosa* in sputum decreased during each of the three 28 day periods of TNS administration and approached baseline during the period when the drug was withheld. It is interesting to note that the treatment effect of TNS on bacterial density was greatest two weeks following the introduction of TNS (average reduction 2.2 log10 cfu/g of sputum) and this progressively decreased by week 20 (average reduction 0.8 log10 cfu/g). The effect of treatment on PA density appears to be influenced by age with the effect decreasing with increasing age. There was a trend towards an increase in the MIC of tobramycin in the PA isolates of patients receiving TNS but not in the placebo group.

Patients receiving TNS were 26% less likely to be hospitalised and 36% less likely to require intravenous antipseudomonal antibiotics than patients receiving placebo. TNS was associated with improvement in global rating of health related quality of life although the magnitude of this effect decreased over time (Quittner *et al*, 2002).

When compared to placebo, TNS was associated with an increased incidence of tinnitus (3.1%) and voice alteration (12.8%). Tinnitus was transient and mild to moderate in severity and did not lead to withdrawal from the study. Voice alteration was minimal in most cases and did not increase with subsequent cycles of TNS administration.

Nine patients in each group had a transient increase of 50% or more in creatinine levels. Audiology studies were carried out in 302 patients. In the 148 patients receiving TNS there was no evidence of hearing loss.

Long term follow up data is now available from the original 24 week trial. A total of 396 patients elected to continue to receive open label TNS. 285 completed 72 weeks and 242 completed 96 weeks (Nickerson *et al*, 1999; Bowman, 2002). While improvements in % predicted FEV1 were maintained above baseline throughout the 96 weeks treatment period, the absolute levels fell from 12.6% at 2 weeks to 9% at 44 weeks 5.4% at 68 weeks and 4.7% at 92 weeks. In patients who had been on placebo, the addition of tobramycin at week 24 resulted in a significant improvement in lung function but at a lower level than those who had been on active treatment throughout the study period.

Moss reported the long term benefits of inhaled tobramycin in a sub group of adolescent patients (Moss, 2002). They found that TNS therapy was associated with increased weight gain and body mass index and that the number of hospitalisations and intravenous antibiotic courses did not increase over the 96 weeks. While improvement in pulmonary function was significantly correlated with reduction in PA colony forming unit density, PA susceptibility to tobramycin appeared to decrease slightly over time. While this did not correlate with clinical response, long term monitoring is required.

Eradication of new isolates of PA

Gibson *et al* conducted a study looking at the microbiological impact of TNS in 98 children aged greater than six years with a positive oropharyngeal culture for PA within two weeks to 12 months before screening (Gibson *et al*, 2003). Following interim analysis of data from the first 21 patients, the study was stopped due to a statistically significant treatment effect. In 23 children who were randomised (eight active) and underwent BAL at baseline and on day 28, there was a significant difference between

treatment group and placebo in the reduction of PA density. No PA was detected on day 28 in those on treatment (n=8). Twelve of the 13 in the placebo group remained *P. aeruginosa* positive. TNS is not recommended for children under six years and further studies are underway to examine the safety and efficacy in this age group.

TNS vs Colomycin

In a randomised clinical trial, Hodson *et al* investigated the efficacy of colomycin and tobramycin nebulised solution in 115 patients with cystic fibrosis who were chronically infected with *P aeruginosa* (Hodson *et al*, 2002). Patients were randomised to receive either TNS (n=53) or colistin (n=62) twice daily for four weeks. Primary end points included the relative change in lung function from baseline. Secondary end points included change in PA density, change in MIC and safety. Only seven patients withdrew from the study, three within the TNS group and four in the colomycin group. Treatment with TNS resulted in a significantly greater improvement in FEV_1 (6.7%) when compared to colomycin (0.37%). Treatment with TNS was also associated with a greater improvement in the global rating of change questionnaire with patients having a relatively greater improvement in medical condition. While this study clearly provides evidence for the effectiveness of TNS, there are a few weaknesses in its design. Firstly, most patients entered into the study were naïve to TNS but many patients had been previously exposed prior to the washout period to nebulised colomycin. This exposure was significantly greater than prior exposure to intravenous or nebulised tobramycin in either group. Furthermore the dose of colomycin used was 1 mu bd which is half the standard dose used by many specialist units in the UK and this may have reduced clinical effectiveness of the drug.

TNS was associated with a mean decrease of 0.86 log10 cfu/ml as compared to 0.60 log10 cfu/ml in colistin treated patients. TNS was associated with 10% increase in the percentage of isolates with a MIC > 4 mg/l (38% to 49%) whereas in the colomycin treated group this remained unchanged. There was no evidence of the development of highly resistant PA in either group.

Pharmacokinetics and bioavailability

Geller *et al* measured tobramycin sputum and serum concentrations, at 10 and 60 minutes respectively during a 20 week study, where 258 patients with CF, received 300mg twice daily in three 28 day on / 28 day off treatment cycles (Geller *et al*, 2002). The mean peak sputum concentrations were 1,237 mμ/g with 95% of patients achieving sputum concentrations > 25 times the minimum inhibitory concentration of PA isolates. One hour after nebulisation, the mean serum concentration was 0.95 mμ/ml. The estimated systemic bioavailability after aerosol administration was 11.7% of the nominal dose. Sputum and serum concentrations of tobramycin did not accumulate over the study period. Although patients gargled three times with 30 ml normal saline, sputum samples may have overestimated drug concentration due to upper airway and oral pharyngeal drug accumulation. Interestingly there was no association between sputum tobramycin concentration and pulmonary function either at week 0 or week 20. However, Gibson *et al* found that at 28 days following tobramycin, BAL samples in children showed drug concentrations ranging from 8.2 to 145.8 mμ/ml at various time intervals from last dose. Serum tobramycin concentrations were also measured as part of the Ramsey study. Median serum concentration was 0.94 mμ/ml (0.18-3.62) at 1 hour post dose (Ramsey *et al*, 1993).

Dosage and administration

TNS comes in a single dose, ready-to-use ampoule containing 300 mg tobramycin. Each box contains a 28-day supply—56 ampoules packaged in 14 foil pouches. Each foil pouch contains 14 ampoules for one week of TOBI therapy.

The 300 mg dose is the same for patients regardless of age or weight.

TNS has not been studied in patients less than six years old.

Doses should be inhaled as close to 12 hours apart as possible and not less than six hours apart.

TNS should not be mixed in the nebulizer with dornase alfa (PULMOZYME®, Genentech). Pulmozyme should not be given within one hour of TOBI therapy.

A bronchodilator such as salbutamol should be considered prior to administration in those individuals who develop bronchospasm. Patients must be formally assessed prior to commencing treatment.

TNS is prescribed in repeated cycles of 28 days on drug followed by 28 days off drug. A dose of 300 mg should be given twice daily during the 28 day period on drug.

The rational for intermittent therapy is based on the observation that a “drug holiday” allows susceptible pathogens to repopulate the airways in patients with cystic fibrosis. However some patients who are declining despite maximal therapy, have been treated by alternating a month of colomycin with a month of TNS, although no clinical data are available to support the efficacy of this approach.

TNS is specifically formulated for inhalation using a PARI LC PLUS™ Reusable Nebuliser and a suitable air compressor with a flow rate of 4-6 l/minute and/or back pressure of 110-217 KPa.

Adverse events.

The incidence of adverse effects in the head to head study with colomycin were comparable for both drugs. Pharyngitis appears to be one of the most common adverse events. Up to 11.3 % of patients on TNS develop an element of airway reactivity with a greater than 10% loss in FEV_1 after 30 minutes of nebulisation. In the study by Ramsey *et al,* TNS was associated with an increase incidence of tinnitus (3.1%) and voice alteration (12.8%). Tinnitus was transient and mild to moderate in severity and did not lead to withdrawal from the study. Voice alteration was minimal in most cases and did not increase with subsequent cycles of TNS administration. Nine patients in each group had a transient increase of 50% or more in creatinine levels. It is not clear from the paper whether these patients had received intravenous antibiotics. Audiology studies were carried out in 302 patients and in the 148 patients receiving TNS there was no evidence of hearing loss.

Although nephrotoxicity did not occur in the randomised studies, acute renal failure has been reported following the administration of inhaled tobramycin and oral ciprofloxacin (Hoffmann *et al*, 2002).

Bronchoconstriction has been well described with both the preservative containing solution and the preservative free solution (Nikolaizik *et al*, 1996; Nikolaizik *et al*, 2002; Alothman *et al*, 2002). Patients should have reversibility studies carried out before starting therapy and monitoring should be continued thereafter. Patients who show bronchoconstriction after drug administration should be prescribed a bronchodilator before each dose. Some patients will not be able to tolerate therapy due to significant bronchoconstriction.

Economic evaluation of TNS

TOBI is expensive, costing up to £10,000 per annum. Studies looking at the economic evaluation of TNS have been undertaken. Iles *et al* concluded in a small study of 42 UK patients receiving TNS for 24 months that treatment was associated with a reduction in hospital attendance and parenteral antibiotics resulting in an offset cost of between £3500 to £6200 (Iles *et al,* 2003). A further study by LeLorier *et al* suggested that assuming that the percentage of reduction in hospital days observed in the US studies would be maintained then the use of TOBI would reduce the use of health care services, particularly hospital days and lead to savings which would offset the cost of the drug (LeLorier*et al* , 2000).

Conclusion

The intermittent administration of TNS in patients with cystic fibrosis and chronic PA colonisation has been shown to be effective in improving and stabilizing lung function, decreasing requirement for intravenous antibiotic therapy and hospital admissions, improving quality of life scores, and in adolescent patients, increasing body weight. Long term microbiological surveillance studies need to be carried out to ensure that significant tobramycin resistance does not ensue.

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