AMBROXOL AND BROMHEXINE INCREASE ANTIBIOTIC LEVELS IN THE LUNGS

Dr. C. Vijai Prasad[1], Dr. M. Abhul Sathar Sait[2], Dr. A. Ponnambalam[1*]

[1]Associate Professor, Department of General Medicine
Sri Venkateshwaraa Medical College Hospital & Research Centre,
Puducherry - 605107

[2]Assistant Professor, Department of General Medicine
Sri Venkateshwaraa Medical College Hospital & Research Centre,
Puducherry - 605107

***Corresponding Author: Dr. A. Ponnambalam,**
Associate Professor, Department of General Medicine, Sri Venkateshwaraa Medical College Hospital & Research Centre,
Villupuram Main Road, Ariyur, Puducherry – 605107.

ABSTRACT

We have searched the literature for evidence of the pharmacokinetics (PK) effect of rifampin. Ambroxol co-administration was proven to be beneficial in the rat model, according to reports. A half-life increase in ambroxol levels in the lung tissue, leading to higher levels of rifampin in the lungs, [5] indicating a double increase in high concentration (Cmax) and an 80% increase in high concentration (Cmax) in mice. Any developments were evaluated in terms of their ability to develop literature. Drug-resistant and drug-resistant germs can be treated. Most pre-clinical trials use complete animals. Despite the fact that lung tissue levels are measured, most clinical studies rely on less invasive procedures such as sputum or bronchoalveolar lavage. In a pre-clinical study, Wiemeyer used mice given 50 mg / kg of oral ampicillin and amoxicillin. with or without oral ambroxol at a dose of 10 mg / kg, compared with the average human dose Ampicillin and amoxicillin tissue concentration increased by 23% and 27%, respectively, with combined ambroxol treatment. However, an increase in the level of antibiotics in the lung tissue is less likely to allow the treatment of antimicrobials, and many doses of antibiotics are already effective in the clinic, so improved effects of ambroxol combination therapy are also not possible. According to at least one clinical report of each class, bromhexine and ambroxol improve the levels of a variety of antimicrobial drugs in the lungs, including beta lactam, erythromycin, rifampin, and vancomycin. Aminoglycosides, fluoroquinolones, sulfonamides, and tetracyclines did not show the same increase, however it is unclear whether this is due to bias in the negative feedback reports or lack of research on these drugs.

KEYWORDS: Ambroxol, Antibiotics, Lungs.

INTRODUCTION

Ambroxol, an active metabolite of prodrug bromhexine, is a popular pain reliever. Out-of-counter medications with a strong safety record have recently been discovered. Both drugs have been reported to enhance the basic process of autophagy [2, 3], however due to low concentration, this action is probably only as important for ambroxol in approved doses. Bromhexine levels are allowed (16 mg TID vs. 30 mg TID for ambroxol) and poor performance of bromhexine is converted to ambroxol. As a result, it was established that ambroxol increased macrophage death at human-relevant doses. Combining ambroxol and rifampin had no impact on Mycobacterium TB infection in mice. The activity of rifampin when used alone in cells was many orders of magnitude greater.

We searched the literature for evidence of this effect being induced by the pharmacokinetics (PK) of rifampin. Ambroxol co-administration was proven to be beneficial in a rat model, according to reports. A half-life increase in ambroxol levels in the lung tissue, leading to higher levels of rifampin in the lungs, [5] indicating a double increase in high concentration (Cmax) and an 80% increase in high concentration (Cmax) in mice. The lower extremity (AUC) was investigated as desirable levels of rifampin were rarely found. Ambroxol may help mycobacteria (NTM) to obtain appropriate levels of rifampin in the lungs when used in standard doses of tuberculosis (TB) [4] or non-tuberculosis to improve clinical care

However, studies reveal that more antibiotics have been identified than rifampin accumulating in large amounts in the lungs. Ambroxol and bromhexine preclinical (1) and clinical data (2) were presented. (2) books, and evaluated any improvements in their ability to develop. Drug-resistant and drug-resistant germs can be treated. Most pre-clinical trials use complete animals. Despite the fact that lung tissue levels are measured, most clinical studies rely on less invasive processes such as sputum or bronchoalveolar lavage (actually redness from infected areas) (bronchoalveolar rejection). Type of BAL liquid wash liquid. To compare preclinical and clinical doses, plasma Cmax for ambroxol was determined.

On the basis of a body weight of mg / kg, a human dose of 30 mg reaches Cmax compared to a human dose of 30 mg, i.e. a human dose of 30 mg gains the same Cmax per human dose of 30 mg. A dose of 30mg / kg was given to mice. [8] Although lung tissue levels may not be easily measured by animal model, collecting human lung tissue samples for these studies is very problematic, which is why most clinical studies use less invasive sampling procedures such as bronchoalveolar disposal. Bronchoalveolar clearance and sputum collection (BAL). Despite the fact that BAL and anti-bacterial levels of sputum are important symptoms, they represent very different matrics for the infection of the lung lumen than the whole lung.

Due to the tissue utilised in most animal research, direct comparisons are impossible. The goal of our strategy was to use ambroxol or bromhexine in PubMed and Google Scholar as one term. antibacterial *, antimicrobial *, antimycobacterial *, or antimycobacterial *, or quinolone *, fluoroquinolone *, macrolide *, aminoglycoside *, or tetracycline *. We also included publications from this study in which we were able to access the full text and which included Antibiotic levels in the lungs and samples taken from the lungs were not counted. There may be more confusing interventions or treatments than two medications.

Effects of ambroxol and bromhexine on antibiotic levels in the lungs :

Lactams (beta lactams):

In a pre-clinical study, Wiemeyer used mice given 50 mg / kg of oral ampicillin and amoxicillin. with or without ambroxol at a dose of 10 mg / kg, compared with the average human dose With ambroxol, the concentration of ampicillin and amoxicillin increased by 23% and 27%, respectively. According to Matsuda et al., Imaoka tested mice given 30 mg / kg of oral ampicillin or cephalexin and found that 1 mg / kg of ambroxol did not significantly increase lung levels, despite the fact that it low dose of ambroxol. [6] Raw cefalothin levels in micrograms / ml were not affected by concentrations of raw protein in horses fed 0.68 mg / kg ambroxol. ambroxol, [10] Taskar et al. looked at the sputum levels in clinics and found that the rate. Patients who received 500 mg of amoxicillin had higher levels of amoxicillin in their sputum. Bronchial production increased from 0.272 g / ml to 0.674 g / ml when 8mg bromhexine was added. [11] BergogneBerezin et al., On the other hand, reported no increase in bronchial discharge with amoxicillin 48 or 96.

Gene et al. found that amoxicillin levels in BAL fluids increased from 0.19 +/- 0.02 micrograms / ml to 0.32 +/- 0.02 micrograms / ml when patients were given 1000 mg orally amoxicillin TID and bromhexine mg every day. [13] Spatola et al. have conducted studies similar to those of Gene et al .'s, except that they examined amoxicillin in implanted lung tissue. The average concentration of amoxicillin in the lungs in the concentration of serum in the blood was significantly higher than 0.41 in the ambroxol group, despite the fact that there was only a tendency to increase amoxicillin in the ambroxol group. Despite the fact that ofloxacin levels in BAL alveolar cells were three times higher, Paganin et al. found no significant increase in BAL levels in those who were given 200 mg ofloxacin twice a day and were given ambroxol.

Individuals given 100 mg of cefixime twice a day (BID) with or without ambroxol were examined by Liu et al. 0.037 mg [16] with the exception of 60 mg ambroxol TID, and it was found that cefixime BAL levels rose from 0.022 to 0.024. Numerous studies have shown a slight increase in beta levels in the lungs.

Ambroxol increased lactam from 23 percent to 68 percent, according to a study by Taskar et al. Bromhexine had a strong effect (148 percent). [11] No significant differences were reported in the three studies. While Paganin et al. had no positive results, Imaoka had the same lack of success. The dose of ambroxol significantly increased lung rifampin levels, while Bergogne-Berezin et al. Bromhexine in low doses was observed to increase erythromycin levels in the lungs. Despite the patient and physician accounts that contradict each other, clinician Askar et al. they were the only ones writing the results.

Responses were improved, but radiological and bacteriological tests did not occur. According to a study from the University of California, the resistance between viral and resistant strains of the virus has increased at least twice since the invention of the reduced beta lactam (MIC). Numerous studies show that using beta-lactam to treat beta-lactam-resistant disease does not work. Because dose enhancement alone would not be sufficient to overcome resistance, a lactam-ambroxol compound was selected. In beta lactam-sensitive disease, the time spent on MIC is strongly associated with bacterial infection. eradication, [17] However, no complete pharmacokinetics were included in any investigation, so it is not clear. It is possible to test whether mixing ambroxol with a beta-blocker improves the levels of beta-blocker. Lactam-resistant pneumonia is still a concern.

Nitrofurans and macrolides:

In pre-clinical studies, mice were treated with 50 mg / kg of oral erythromycin with or without 10 mg / kg of oral erythromycin. Ambroxol increased the concentration of lung tissue by 27% in mice, according to research. Ambroxol (2 mg / kg) was added to roxithromycin (10 mg / kg) to improve lung capacity. [18] Lee found that tissue levels of roxithromycin in mice varied from 3.20 to 4.06 g / ml in the same study.

According to Choi, 10 mg / kg clarithromycin increased the bioavailability of 12 mg ambroxol by 71 percent, [19] probably due to its activities as a cytochrome P450 3A4 inhibitor. An enzyme that stimulates the metabolism of ambroxol. [20] The effect of ambroxol on clarithromycin in the lungs. Rates, on the other hand, were not stated. Bergogne-Berezin et al. found that those given Bronchial clearance improved when bromhexine (8 mg TID) was added to 500 mg erythromycin BID.

The rate of erythromycin release from serum increased from 0.24 to 0.434. [12] In chickens given 50 mg / kg of furaltadone, bromhexine or ambroxol was detected. The doses of the furaltadone control group alone were 0.875 and 1.75 mg / kg. Ambroxol use that led to Furaltadone levels in tracheobronchial production increased in a dose-dependent manner from 3.1 to 5.6. 7.2 mg / g, respectively, while bromhexine doses only caused an increase of 3.1 to 3.9 mg/g. [21]

Glycopeptides and rifamycins

In mice given rifampin PO of 50 mg / kg, Imaoka found that simultaneous use of 1 mg / kg ambroxol increased rifampin Cmax in the lung tissue from 9.48 to 22.47 g / ml after 4 hours. , and increased AUC0-24h from 99 to 178. g * h / l. According to Zhang et al., Lung levels mean 1, 2, and 4 hours in rats IV given rifampin 30 mg / kg were 31.8, 15.2, and 6.2 g / ml, respectively. Rifampin lung levels increased by 15 mg / kg IV ambroxol pretreatment to 35.5, 25.6, and 13.6 g / ml simultaneously, resulting in greater rifampin retention and possibly higher AUC.

Expert Advice

The levels of antibiotics in the lung tissue are less likely to treat organisms that are resistant to the same class of antibiotics, and many doses of antibiotics are already clinically effective, so better effects of ambroxol combination therapy may also be possible. However, in the treatment of TB and NTM with rifampin, as well as MRSA pneumonia with vancomycin, the usual doses are largely determined by the toxicity of the drug as it is clinically effective, making simply increasing the dose of these antibiotics to increase lung levels difficult. However, ambroxol has caused an increase in the levels of rifampin and vancomycin without increasing the dose of antibiotics, suggesting that the drug may offer significant therapeutic benefits without increasing the dose-related side effects. Ambroxol may also help prevent rifampin resistance to growth. Because ambroxol is currently on the market, testing these ideas could be accomplished much faster than inventing new antibiotics. However, a number of concerns remain unresolved, such as what ambroxol dose should be used with rifampin or vancomycin. Although chickens given only a veterinarian antibiotic showed a dose response, it was the only dose response of ambroxol. In the future, the field should focus on the lack of comprehensive knowledge of pharmacokinetic effects, particularly in humans, as well as bacteriological and clinical effects.

The problem of co-administration of ambroxol with rifampin is complicated by the activation of cytochrome P450 3A4 (Cyp3A4) by rifampin and the ambroxol sensitivity to Cyp3A4 metabolism. [20] Rifabutin is used to resist Cyp3A4, ambroxol deuteration is used to resist Cyp3A4, Cyp3A4 inhibition is used to overcome this, and high doses of ambroxol are used to overcome this.

CONCLUSION

According to at least one clinical report of each class, bromhexine and ambroxol improve the levels of a variety of antimicrobial drugs in the lungs, including beta lactam, erythromycin, rifampin, and vancomycin. Aminoglycosides, fluoroquinolones, sulfonamides, and tetracyclines did not show the same increase, however it is unclear whether this is due to bias in the negative feedback reports or lack of research on these drugs. The effective doses of ambroxol in rodent preclinical models ranged from 1 mg/kg to 16 mg/kg, equivalent to Cmax obtained by lower human doses in comparison; therefore, this pre-clinical research organization indicates the appropriate doses of human ambroxol. In addition to the experiments in chickens, clinical trials used total doses of ambroxol ranging from 15 to 180 mg/day and bromhexine from 8 to 96 mg/day, although there was no dose response or any clear pattern for any response. of volume was not clearly stated.

REFERENCES:

1. Van Ingen J, Aarnoutse RE, Donald PR, et al. Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment? Clin Infect Dis. 2011. May;52(9):e194–9.
2. Zhang Z, Yang C, Tu W. Effect of ambroxol on the transport of rifampicin into pulmonary. Jiangsu Medical Journal. 2009;35(12):1486–8.
3. Preclinical Imaoka M. and clinical investigation about combination effects of expectorants in chemotherapy of infectious respiratory diseases. Chemotherapy. 1986;34(3):262–70.
4. Van Ingen J, Egelund EF, Levin A, et al. The pharmacokinetics and pharmacodynamics of pulmonary Mycobacterium avium complex disease treatment. Am J Respir Crit Care Med. 2012. September 15;186(6):559–65.
5. Gaida W, Klinder K, Arndt K, et al. Ambroxol, a Nav1.8-preferring Na(+) channel blocker, effectively suppresses pain symptoms in animal models of chronic, neuropathic and inflammatory pain. Neuropharmacology. 2005. December;49(8):1220–7.
6. Wiemeyer JCM. Influence of Ambroxol on the Bronchopulmonary Level of Antibiotics. Arzneimittel-Forsch. 1981;31-1(6):974–976.
7. Matsuda Y, Hobo S, Naito H. Transferability of cephalothin to the alveolar cavity in thoroughbreds. The Journal of veterinary medical science. 1999. March;61(3):209–12.
8. Taskar VS, Sharma RR, Goswami R, et al. Effect of bromhexeine on sputum amoxycillin levels in lower respiratory infections. Respiratory medicine. 1992. March;86(2):157–60.
9. Bergogne-Berezin E, Berthelot G, Kafe HPJ, et al. Influence of a Fluidifying Agent (Bromhexine) on the Penetration of Antibiotics into Respiratory Secretions. Int J Clin Pharm Res. 1985;5(5):341–344.
10. Gene R, Poderoso JJ, Corazza C, et al. Influence of ambroxol on amoxicillin levels in bronchoalveolar lavage fluid. Arzneimittelforschung. 1987. August;37(8):967–8.
11. Spatola J, Poderoso JJ, Wiemeyer JC, et al. Influence of ambroxol on lung tissue penetration of amoxicillin. Arzneimittelforschung. 1987. August;37(8):965–6.

12. Paganin F, Bouvet O, Chanez P, et al. Evaluation of the effects of ambroxol on the ofloxacin concentrations in bronchial tissues in COPD patients with infectious exacerbation. Biopharmaceutics & drug disposition. 1995. July;16(5):393–401.
13. Liu S, Qing D, Zhang W. Influence of ambroxol on cefixime levels in bronchoalveolar lavage fluid. Chinese Journal of Hospital Pharmacy 1998;18(9):387–8.
14. Turnidge JD. The pharmacodynamics of beta-lactams. Clin Infect Dis. 1998. July;27(1):10–22.
15. Wang P, Qi M, Jin X. Determination of roxithromycin in rat lung tissue by liquid chromatography-mass spectrometry. Journal of pharmaceutical and biomedical analysis. 2005. September 15;39(3-4):618–23.
16. Lee CK, Choi JS. Effect of Clarithromycin on the Pharmacokinetics of Ambroxol in Rats. Journal of Pharmaceutical Investigation 2006;36(3):157–60.