Estimation of a Drug Effect by a Simplified Radioaerosol Inhalation Lung Cine-Scintigraphy: Bromhexine on Mucociliary Clearance Mechanisms

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Isawa, T., Teshima, T., Hirano, T., Ebina, A. and Konno, K. Estimation of a Drug Effect by a Simplified Radioaerosol Inhalation Lung Cine-Scintigraphy: Bromhexine on Mucociliary Clearance Mechanisms. Tohoku J. exp. Med., 1986, 148 (2), 163–167 — A proposed simplification of radioaerosol inhalation lung cine-scintigraphy, namely 60 min measurement of radioactivity without repeating measurement at 24 hr later and calculation of alveolar deposition ratio (ALDR) by the regression formula of ALDR = -48.08 + 0.47 × FEV1.0% + 0.59 × LRR60, was found useful and applicable even to the evaluation of a drug on mucociliary clearance mechanisms. The simplified method indicated a very similar evaluation of the effect of bromhexine on airway clearance efficiency with those actually revealed by the original method.

Radioaerosol inhalation lung cine-scintigraphy for visualization of mucociliary clearance mechanisms in the lungs and five indexes for quantitative evaluation have facilitated the understanding of mucociliary clearance function in the lungs (Isawa et al. 1981, 1984 a, b).

In a previous communication we have reported regression functions to estimate the alveolar deposition ratio (ALDR) of inhaled aerosol (Isawa et al. 1985). There the ALDR was the amount of radioactivity remaining in the lungs at 24 hr in per cent as compared with the initial radioactivity in the lungs immediately after inhalation of radioactivity; in other words, lung retention ratio at 24 hr. If these regression functions are really usable and clinically applicable, we can shorten the measuring time after aerosol inhalation from 120 min as originally proposed (Isawa et al. 1981) to 60 min and do not have to repeat measurement of remaining radioactivity at 24 hr. One of the regression functions applicable both to the patients and normals is ALDR = -48.08 + 0.47 × FEV1.0% + 0.59 × LRR60.
which requires as variables only FEV1.0% or forced expiratory volume in one sec divided by forced expiratory volume in per cent and LRR60 or lung retention ratio at 60 min (Isawa et al. 1985).

The purpose of the present report is to determine whether or not the evaluation of a drug effect by applying the regression function to estimate the ALDR reveals similar results with that by actual measurement.

MATERIALS AND METHODS

Ten patients with various chest diseases in stable stage were studied before and after the administration of bromhexine 8 mg t.i.d. per orally for 7 days. The details of the data including the patients' illness, their cine-scintigraphic findings, lung retention ratio (LRR), airway deposition ratio (ADR), airway retention ratio (ARR), airway clearance efficiency (ACE) and ALDR have been already published elsewhere (Isawa et al. 1984 c). In short, the LRR's represent the overall radioactivity remaining in the lungs in per cent during each 10 min as compared with the radioactivity during the initial 10 min, whereas the ALDR is equivalent to the LRR at 24 hr. The ADR is the amount of radioactivity throughout the ciliated airways relative to the total radioactivity initially deposited in the lungs. The ARR's indicate what percentage of radioactivity initially deposited on the ciliated airways still remains there at time t. The ACE's indicate what percentage of the radioactivity deposited on the ciliated airways has already been cleared by time t (Isawa et al. 1984 a). By using the published FEV1.0% and lung retention ratio at 60 min (LRR60), we estimated the ALDR following the regression function of ALDR = -48.08 + 0.47 × FEV1.0% + 0.59 × LRR60 (Isawa et al. 1985).

By using the observed LRR up to 60 min and the fitted ALDR, the ADR, the ARR and the ACE were calculated for each patient before and after bromhexine administration up to 60 min.

Statistical evaluation was made by paired t-test and chi-square \((\chi^2)\) test (Swinscow 1977). In evaluating the drug effect, the difference in ACE equal to or more than 3 percent before and after administration was taken as significant and the difference equal to or less than 2 percent as no change.

![Fig. 1. Observed vs. fitted calculated alveolar deposition ratio (ALDR). The latter was calculated following a regression function of ALDR = -48.08 + 0.47 × FEV1.0% + 0.59 × LRR60. The correlation coefficient \((r)\) was 0.629 with \(p\) less than 0.01.](image)

\(\bigcirc\), before bromhexine; \(\bullet\), after bromhexine.
RESULTS

Alveolar deposition ratio (ALDR)

There was no statistical difference between the ALDR actually observed and the fitted one by paired t-test as shown in Fig. 1. The correlation coefficient ($\rho$) was 0.629 with $p < 0.01$. 

Fig. 2. Observed airway clearance efficiency (ACE) versus fitted ACE. Mean±s.e. There is no statistical difference between the actual and estimated ACE by paired t-test.

Fig. 3. Comparison of airway clearance efficiency (ACE) in case no. 1 by actual measurement and by estimation before (○) and after (●) the administration of bromhexine. There was virtually no difference between the actual and the estimated ACE.
Airway deposition ratio (ADR), airway retention ratio (ARR) and airway clearance efficiency (ACE)

There was no statistical difference between the fitted values based on the LRR and the observed ALDR's or the fitted ALD's in any of the three indexes. The relationships in ACE is shown in Fig. 2.

Evaluation of drug effect

The ACE up to 60 min before and after the administration of bromhexine was plotted separately for the fitted values based on the observed ALDR and the observed LRR and the estimated ones based on the fitted ALDR and the LRR at each corresponding time interval as shown in Fig. 3 as an example.

According to chi-square test the distribution of chi-square was nearly identical with each other before and after bromhexine administration as shown in Table 1, indicating that the evaluation of the drug effect from the fitted ALDR was similar to that based on the observed ALDR.

DISCUSSION

Previously we reported that bromhexine was statistically significant in increasing the airway clearance efficiency (ACE) based on the continuous 2 hr measurement for calculating lung retention ratios (LRR) and the repeat measurement of radioactivity at 24 hr to get the actual alveolar deposition ratio (ALDR). The continuous 2 hr measurement, however, is too long in duration for a clinical examination and the repeat measurement at 24 hr is also cumbersome both to the examinee and the examiner. Because ALDR was estimable by means of a regression equation using FEV1.0% and LRR60, the measuring time seemed possible to be shortened from 120 to 60 min (Isawa et al 1985)

In this communication we tried to see whether the comparison of the airway clearance efficiency (ACE) estimated by using the observed ALDR and the fitted ALDR before and after the administration of bromhexine could really result in

Table 1. The distribution of $\chi^2$ values and probability of error in the evaluation of bromhexine; actual versus estimated

<table>
<thead>
<tr>
<th>Time after inhalation (min)</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual</td>
<td>3.80</td>
<td>3.20</td>
<td>7.40</td>
<td>7.40</td>
<td>7.40</td>
</tr>
<tr>
<td>Probability of error ($p$)</td>
<td>0.10 $&lt; p &lt; 0.50$</td>
<td>0.10 $&lt; p &lt; 0.50$</td>
<td>0.02 $&lt; p &lt; 0.05$</td>
<td>0.02 $&lt; p &lt; 0.05$</td>
<td>0.02 $&lt; p &lt; 0.05$</td>
</tr>
<tr>
<td>Estimated</td>
<td>3.20</td>
<td>3.20</td>
<td>7.40</td>
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Effect of Bromhexine on Mucociliary Clearance Mechanisms

similar evaluation of the drug effect or not. It turned out to be practically identical as indicated in Figs. 1, 2 and in Table 1. The distribution of chi-square was identical after 30 min. It might seem from the above discussion that the 30 min measurement is then enough for the evaluation of a drug effect, but it is not necessarily so, because compilation of radioaerosol inhalation lung cine-scintigraphy adequate enough for visual evaluation of the mucociliary clearance mechanisms in the lungs requires a certain number of frames. Mucociliary clearance mechanisms are rather slow phenomena so that the longer the measuring time, the more facets of the mechanisms are expected to be explored. The 60 min measurement resulting in 360 frames if 10 sec frame each is secured seems to be a reasonable compromise in this respect. By this simplification, both the visual or qualitative and the numerical or quantitative evaluations of mucociliary clearance mechanisms by looking at radioaerosol inhalation lung cine-scintigraphy and analysing the time activity curve of the lung region with the aid of the fitted ALDR, respectively, would not only facilitate our understanding of the mucociliary clearance mechanisms in the lungs in health and disease but also be applicable to the objective evaluation of the effect of a drug or a therapeutic modality.

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References


