Intensive Care Med (1997) 23: 992–997

C. Aufricht
F. Votava
M. Marx
K. Frenzel
G. Simbruner

Intratracheal furosemide in infants after cardiac surgery: its effects on lung mechanics and urinary output, and its levels in plasma and tracheal aspirate

Received: 14 February 1997
Accepted: 15 May 1997

This study was sponsored by HOECHST AG, Frankfurt/M, Germany and "Fonds des Buergermeisters der Landeshauptstadt Wien", Austria

C. Aufricht · F. Votava · M. Marx · K. Frenzel
Universitäts-Kinderklinik,
University of Vienna, Vienna, Austria

G. Simbruner (✉)
Universitäts-Kinderklinik
Dr. v. Haunersches Kinderspital,
Lindwurmstrasse 4, D-80337 Munich, Germany
FAX: + 49 (89) 51604419

Abstract *Objective:* Recent studies have suggested direct pulmonary effects of furosemide in asthmatics and infants with bronchopulmonary dysplasia. We tested the hypothesis that intratracheally administered furosemide also increases respiratory compliance in children after cardiac surgery, and investigated whether furosemide has a topical and/or systemic action.
Study design: Prospective study with intra-individual control. In twelve infants and toddlers (age: 10 ± 8 months, weight: 6.9 ± 3 kg) mechanically ventilated for compromised lung mechanics after cardiac surgery, 0.5 mg/kg furosemide was intratracheally administered to the lungs. Lung mechanics were serially assessed using a computerised system (Sensormedics 2600) during a 2 h control and 2 h intervention period. Urine output was measured by an indwelling bladder catheter and levels of furosemide were determined in blood and tracheal aspirates.
Results: Static compliance improved within 30 min in all patients, reached a maximum of 44 (20–85) % above baseline and remained improved throughout the study ($p < 0.05$). An immediate, short and significant diuretic effect of intratracheally applied furosemide was observed. Furosemide levels 1 h after intervention were 795 ng/ml in the blood and 431 μg/ml (i.e. 1000-fold higher) in the tracheal aspirate. Changes in compliance were correlated only to urine output values over the 2 h ($r = 0.82$, $p = 0.044$, $n = 9$) after furosemide administration.
Conclusion: We conclude that intratracheally applied furosemide improves static compliance in infants and toddlers with compromised lung mechanics after cardiac surgery. We demonstrated that furosemide is absorbed from the lung and has a systemic effect within 15 min after its intratracheal instillation.

Key words Topical furosemide · Lung mechanics · Plasma levels

Introduction

Postoperative lung mechanics are often compromised after cardiac surgery for the repair of congenital heart disease. Decreased compliance and increased airway resistance of the respiratory system, due to increased lung water content, are considered to be responsible for the difficulty of weaning these patients from the respirator postoperatively. Consequently current therapeutic interventions are directed towards, amongst others, a negative total body water balance and diuretics are administered to reduce total body, including lung, water content [1–3].

A selective reduction of pulmonary water by drugs which act directly at the lung, as target organ, would be a major therapeutic achievement. In recent studies in-

tratracheal administration of furosemide has been shown to attenuate bronchospasm in adult and pediatric asthmatics, effects which were specific for inhaled furosemide and not seen with intravenous and oral administration [4–6]. Furosemide was also found to relax the airway and vascular smooth muscles independent of cyclooxygenase blockade or endothelial removal [7]. These topical effects appear to be more pronounced in the less mature guinea pig [7]. Recently, Rastogi et al. and Pabhu et al. demonstrated that inhaled furosemide increased compliance in infants with bronchopulmonary dysplasia (BPD) up to 50% without causing significant systemic effects [8, 9]. However, the theory of topical action has already been challenged by the demonstration of rapid absorption of intratracheal furosemide from the lung into the blood in guinea pigs [10]. Because some investigators failed to confirm the effect with inhaled furosemide in intubated infants [11], instillation of furosemide into the trachea (i.e. intratracheally) in a manner similar to surfactant introduction, was chosen as the mode of administration [12].

We therefore tested the hypothesis that intratracheally administered furosemide would also increase respiratory compliance after cardiac surgery in children with compromised lung mechanics, presumably due to increased pulmonary water accumulation. In particular, we were interested 1) in the relationship of lung mechanics to urinary output changes and 2) in the levels of furosemide in plasma and tracheal aspirates, to challenge the theory of "topical effect only".

Patients and methods

Twelve infants (8 boys and 4 girls, with a median age of 7 months (mean 10.0; range 0.3–13.2 months, weight at study 6.9 ± 3 kg; mean ± SD) with unremarkable pulmonary history, who underwent cardiac surgery for repair of congenital heart disease and who were mechanically ventilated due to compromised lung mechanics, were enrolled in the study. Seven children with left-to-right shunts (two ventricular, three atrial and ventricular and two ductal shunts), one child with transposition of the great arteries and one child with critical aortic stenosis underwent anatomical correction. In three cyanotic children (1 tricuspidal, 2 pulmonal atresia) palliative systemicopulmonal shunts were performed.

These infants were studied at a median age of 2 days postoperatively (range 1–7 days). All patients had radiographic signs of interstitial edema and were hemodynamically stable on vasopressors. No patient suffered from postoperative infection, as indicated by re-elevation of body temperature, leukocytes, cross-reacting protein or positive blood culture. All patients were intubated with uncuffed tubes and ventilated with the Babylog 8000 (Draeger, Lübeck, Germany). This device assesses inspiratory and expiratory tidal volumes on line by a hot wire anemometer and computes tube leakage. No patients exhibited any air leak during the study. Eight children were paralyzed with pancuronium, the other four breathed spontaneously and were sedated with midazolam. The pulmonary disease status of these 12 patients was homogeneous as judged from the statistical variation of fraction of inspired oxygen 0.4 ± 0.1 to obtain normal blood gases, of the ventilator settings and compliance at the beginning of the study. The patients were on positive pressure ventilation with peak inspiratory pressure 23 ± 3 cm H_2O, tidal volume 10.8 ± 2.2 ml per kg body weight; positive end expiratory pressure 2.5 ± 1 cm H_2O, frequency 20 ± 9 min^{-1} and inspiratory time 0.65 + 0.1 s. Their compliance (for methods, see below) was 0.56 ml/cm H_2O per kg body weight initially. The study was approved by the local Ethical Committee and informed consent was obtained from the parents.

Study protocol

We measured lung mechanics and urinary output as end-point variables of the intervention, determined the associated furosemide levels in plasma and tracheal aspirates, and monitored heart rate, blood pressure and pulse-oximetry as safety variables during the study period. After a control period of 2 h with measurements of the variables at the beginning (–120 min) and immediately before (0 min) the intervention, furosemide was administered intratracheally. Furosemide at a dosage of 0.5 mg/kg body weight was injected via a thin catheter, slightly longer than the intratracheal tube, into the airways, in a similar way to the administration of surfactant in ventilated neonates. The furosemide was injected in its original concentration of 10 mg/ml solution i.e. in volumes ranging from 0.2 to 0.6 ml. It had a pH of 8–9.3. The above-described set of variables was again measured after 15, 30, 60 and 120 min following the first intratracheal administration of furosemide in all infants. All medications, fluid input and respirator settings were protocolled. During a 4 h study period (2 h control and study period) the attending intensive care doctors were asked not to alter the respiratory settings and to avoid any other interventions which would specifically affect the study variables.

Nine of the 12 infants who received no other diuretics except the intratracheal furosemide after the control period formed the main study group. Three of the 12 infants were on continuous intravenous furosemide medication during the whole study period but, in addition, received intratracheally administered furosemide like the other nine patients.

Lung mechanical measurements

Lung mechanics were measured during passive exhalation into the atmosphere by means of a computerised device (Sensormedics 2600, SensorMedics, USA). This commercially available device has a pneumatically driven valve with a dead space of 5.9 ml inserted into the ventilator circuit, which occludes, computer-controlled, the tracheal tube and airways at the end of a mechanical inspiration for 0.3 s to determine the relaxation pressure, and then opens the valve to measure expiratory flow to the atmosphere by means of a pneumotachograph (Hans Rudolph, Kansas City, MO). Airway pressure was measured by a pressure transducer (Validyne MP45, + / – 40 cm H_2O) connected to a side port of the naso tracheal tube adaptor and flow by a differential pressure transducer (Validyne MP 45, + / – 2 cm H_2O; Validyne Corp., Northridge, CA). Airway pressure and flow were recorded on-line by a microcomputer (IBM PS/2 Model 50) and an analogue-to-digital converter (Data Translation DT 2801; sampling frequency, 256 samples/s). The expiratory flow was integrated to volume and displayed as a passive flow-volume loop. Curves were accepted for analysis if the pressure plateau was stable and the flow-volume relationship during expiration was linear. Values were calculated as the mean of at least 8 acceptable curves recorded at each measurement session. The system was calibrated before each study by a wa-

ter manometer for pressure and by a 100 ml syringe for flow/volume measurements. During measuring intervals, the infants were ventilated through the valve.

Urine output

was measured by indwelling bladder catheters to decrease the time delay. Urinary output was assessed for time periods varying between 15, 45, 60 and 120 min during the study and normalised for body weight.

Tracheal aspirates

were obtained by a routine tracheal suction procedure (through a mucous trap) from nine patients at 0 and 60 min post-intratracheal furosemide administration.

Blood samples for plasma furosemide

were collected in nine patients (main group) at 0, 15, 30, 60 and 120 min post-intervention and furosemide levels could be analysed for eight of these patients. Furosemide levels were measured at the Hoechst research laboratory.

Data analysis

The differences between data cohorts were tested by analysis of variance, differences between single time points by Wilcoxan signed rank test and correlations between variables by parametric and non-parametric tests (linear or polynomial regression and Spearman correlation coefficient). The results are expressed as the mean ± standard deviation (mean ± S.D.). Changes in static compliance and in urinary output were also expressed as percentages of the baseline.

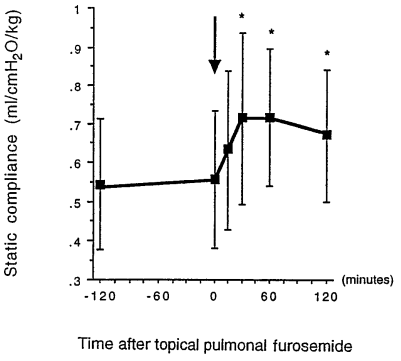

Fig. 1 Time course of static lung compliance (mean ± standard deviation) after intratracheal administration of furosemide in 12 mechanically ventilated infants and toddlers with compromised lung mechanics after cardiac surgery. The compliance values increased within 15 min and this effect lasted throughout the observation period of 2 h. $n = 9$, * $p < 0.05$

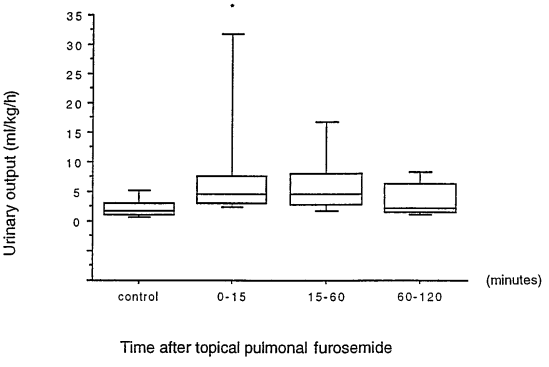

Fig. 2 Box and whiskers plot of urinary output after intratracheal furosemide in 12 mechanically ventilated infants and toddlers after cardiac surgery. Diuresis was increased during the first 15 min after administration of intratracheal furosemide. n = 9, * $p < 0.05$

Results

Main group of nine patients receiving intratracheal furosemide only

During the 2 h control period static respiratory compliance was 0.54 ± 0.18 ml/cm H_2O per kg and quite stable (the coefficient of variation being only 5.8 ± 5). Total respiratory resistance did not change either. After intratracheal administration of furosemide, the increase in compliance was statistically significant ($p < 0.05$), the maximal increase amounting to 44% (range 20–85%). The first response was observed within 15 min in 7/9 and at 30 min in 9/9 patients. Maximal compliance was observed within 60 min in all patients (Fig. 1). The change in resistance, initially 76 ± 58 cm H_2O/l per sec, was not statistically significant at any time during the study, but average values were 20–30% lower 2 h after intratracheal furosemide medication.

Urine output was 2.3 ± 1.8 ml/kg during the control. It significantly increased within 15 min to maximal values ($p < 0.05$) and fell again to lower values at 120 min (Fig. 2). Urinary output in response to intratracheal furosemide was related to the urinary output during the control period. The lower the urine output before, the higher the output at 15 min (in patients with < 2 ml/h per kg during control, it increased up to 16-fold; in patients > 2 ml/h per kg during control, it increased only by an average of 22%). Compliance at 15, 30 or 60 min did not, but at 120 min after intratracheal furosemide did significantly correlate with urine output values over those 2 h ($r = 0.82$, p = 0.044, $n = 9$).

The intratracheal instillation of the low volume of furosemide (< 0.6 ml) did not cause any cough, significant desaturations or other side effects. In the three infants who had received furosemide intratracheally in addition to a continuous i.v. furosemide, compliance increased in a manner similar to that of the main group

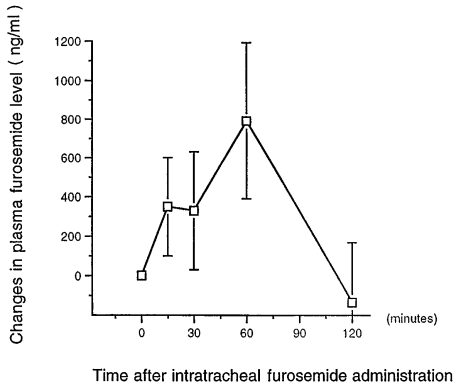

Fig. 3 Time course of plasma furosemide levels after intratracheal administration of 0.5 mg furosemide in eight infants

(+ 20 % at 15 min, + 40 % at 30 min, + 17 % at 60 min and + 30 % at 120 min).

Furosemide levels in plasma and tracheal aspirate

Furosemide levels in plasma increased to 380 ng/ml at 15 min and reached their maximum of 795 ± 387 ng/ml at 60 min (Fig. 3). The plasma levels achieved with intratracheal administration increased urinary output from about 2.3 to 4.5 ml/kg over the first 2 h. Systemic furosemide levels at no time significantly correlated with changes in urine output or respiratory compliance. Furosemide levels in the tracheal aspirate at 60 min after its topical administration were a 1000 times higher (431 μg/ml, range 0–1200 μg/ml) than those in the blood. Furosemide levels in the tracheal aspirate did not correlate to the compliance changes ($r = 0.382$, $p = 0.31$, $n = 9$).

No significant acute side effects of the intratracheal administration of furosemide on variables related to oxygenation were observed. Heart rate, blood pressure and pulse oxymetry were stable throughout the study. Three children had short (10–20 s) periods of decreases in saturation in pulse oximetry immediately after the administration of intratracheal furosemide.

Discussion

Our study demonstrates that furosemide applied to the respiratory surface in a dose of 0.5 mg/kg body weight significantly increased static lung compliance in all 12 mechanically ventilated infants and young children with compromised lung mechanics after repair of congenital heart disease. Furosemide, intratracheally administered, results in an immediate and short increase in the rate of urine output, followed by an improvement in respiratory compliance, the increase of which is related to urine output at 2 h.

We emphasize that the aim of the prospective study with intra-individual control was primarily to investigate whether furosemide administered intratracheally to the lungs had any effect at all on lung mechanics in patients with abnormal lung parenchyma (interstitial edema) and whether a systemic effect could be detected through the use of catheter-monitored urinary flow (instead of urine assessment by napkin weighing or urine bag collection). We did not investigate whether furosemide instilled into the trachea in the same way as a surfactant had a greater or smaller effect than intravenous furosemide, because we thought it important to demonstrate that there was some effect of intratracheal furosemide. Furthermore, we considered the instillation of up to 0.6 ml into the airway was not a maneuvre which would significantly affect lung mechanics, and if it did, then it would definitely not result in an acute improvement. The long-term local effects of intratracheally administered furosemide are unknown and warrant investigation. Inhaled furosemide has never been reported to be toxic [4–6, 8, 9]. Should intratracheally administered furosemide have a specific topical effect, this mode of administration should be considered only in infants with bronchopulmonary dysplasia (BPD) or other parenchymal diseases in whom local effects are desired, and not in infants with cardiac disease needing a systemic effect.

Intratracheal furosemide increased lung compliance by about 50 % within 1 h after administration. Following the initial observation of Bianco et al. several reports have confirmed an effect of topically administered furosemide on airway constriction and, primarily, obstructive lung diseases like asthma. In asthmatic adults and children, inhalation of furosemide inhibited airway constriction after various bronchoconstrictory stimuli [4–6]. No effects could be demonstrated in adult asthmatic patients with an acute attack, compromised lung mechanics and parenchymal disease [13]. However, in infants with BPD, which is also associated with decreased compliance, topically applied furosemide has been reported to increase compliance significantly [8, 9]. These investigators reported an up to 50 % improvement in lung mechanics within the first 2 h after inhalation of 1 mg/kg furosemide, unaccompanied by increased diuresis [8, 9]. Our study confirms this finding that topically administered furosemide improves lung mechanical function, and extends this to a patient population with a different disease mechanism most probably associated with increased water content in the lungs, which are not deficient in surface active material. The instillation of half the dose (0.5 mg/kg) of furosemide into the trachea achieved an equally effective compliance increase (+ 44 %) to inhalation of 1 mg/kg furosemide in the studies of Rastogi et al. and Pabhu et al. (+ 51 % and + 30 %).

Furosemide was rapidly absorbed from the respiratory epithelium, because a distinct increase in urine out-

put, compared to control, and a plasma furosemide level of 400 ng/ml were observed within the first 15 min. The plasma levels of 400–700 ng/ml of furosemide at 15 min and 1 h, respectively, were lower than those of 2–4 μg/ml observed in newborns after a single intravenous dose of more than 1.0 mg/kg [14, 15]. These furosemide levels nevertheless yielded a considerable increase in urine output from 2.3 ml/kg to about 4 ml/kg over 2 h. Intratracheal and intravenous administration of furosemide, according to an experimental study in guinea pigs, resulted in similar plasma levels at 1 h after administration and the fractional absorption reached about 50–60 % of the amount intratracheally instilled [10]. We therefore conclude that the intratracheal route is an effective mode of furosemide administration and more reliable than inhalation. Some investigators administering inhaled furosemide to intubated newborns with respiratory distress syndrome might have failed to confirm a furosemide effect, because of loss of the inhaled medication in the tracheal tube [11].

The high concentration of 430 μg/ml furosemide in the tracheal aspirate after 1 h was still 1000 times higher than in the blood. This high concentration could have resulted from sampling it in the airways to which it was administered. Provided the sample was representative of an average concentration in the bronchial tree, most of the intratracheally instilled furosemide, known to be highly protein-bound, might have been bound in the edematous bronchoalveolar fluid. Because of retarded absorption, the peak plasma furosemide might have occurred much later (60 min after intratracheal instillation) than in guinea pigs, where peak furosemide levels were observed 10 min after tracheal instillation. As renal furosemide clearance in infants older than 3 months is similar to that of guinea pigs [10], the delayed peak in our infants with assumedly normal surfactant is most probably due to a delayed absorption from the broncho-alveolar space.

Whether intratracheally administered furosemide has a topical effect or just exerts its effect systematically after rapid absorption into the pulmonary circulation, or both, remains unanswered by this study. Most of our observations indicate that intratracheally administered furosemide acts via systemic diuresis. Our study demonstrates improvement in compliance within 15 min in some and at 30 min in all patients, in parallel with the highest increase in urine output within the first 15 min. The fact that compliance changes were not significantly related to rates of urine output during the first hour, but only to cumulative urine output after 2 h, does not speak against a systemic effect. In addition, the lack of a relationship between compliance and urine output described in other investigations does not exclude systemic effect, because either monitoring of the urine output was not directly assessed via a bladder catheter, or it was sampled over too long a period to detect small changes, or the absorbed dose of the inhalate might have been too small to alter urinary flow significantly [8, 9]. Further studies are required to elucidate the complex relationship between furosemide absorption and clearance, its diuretic action and the redistribution of extracellular water.

The demonstration of a systemic effect does not exclude a topical effect of furosemide. Several publications report specific effects of furosemide on ion and water transport via Na^+K^+ cotransport, carbonic anhydrase inhibition, PGE_2 production and other furosemide sensitive mechanisms [16–19].

We conclude that intratracheally administered furosemide results in significant improvement in the lung mechanics of infants and toddlers with compromised lung mechanics after cardiac surgery for repair of congenital heart disease. A direct assessment of urinary output and measurement of furosemide in the plasma and tracheal aspirate indicate a predominantly systemic effect.

Acknowledgements This study was in part financed by "HOECHST" and the "Fonds des Buergermeisters der Landeshauptstadt Wien". We thank Dr. Verho and HOECHST laboratories for their support.

References

1. Vincent RN, Lang P, Elixson EM, Gamble WJ, Fulton DR, Fellows KE, Norwood WI, Castaneda AR (1984) Measurement of extravascular lung water in infants and children after cardiac surgery. Am J Cardiol 54: 161–165
2. Rowe RD (1978) Tetralogy of Fallot. In: Keith JD, Rowe RD, Vlad P (eds) Heart Disease in Infancy and Childhood. 3rd ed. Macmillan, New York, p 496
3. Lister G, Talner NS (1981) Management of respiratory failure of cardiac origin. In: Gregory GA (ed) Clinics in critical care. Churchill Livingstone, New York, pp 67–88
4. Bianco S, Vaghi A, Robuschi M, Pasargiklian M (1988) Prevention of exercise induced bronchoconstriction by inhaled furosemide. Lancet 2: 252–255
5. Roger A, Botey J, Eseverri JL, Marin A (1993) Prevention of exercise-induced asthma in children using low doses of inhaled furosemide. J Invest Allergol Clin Immunol 3: 300–303
6. Seidenberg J, Dehning J, Von der Hardt H (1992) Inhaled furosemide against cold air-induced bronchoconstriction in asthmatic children. Arch Dis Child 67: 214–217

7. Stevens EL, Uyehara FT, Southgate WM, Nakamura KT (1992) Furosemide differentially relaxes airway and vascular smooth muscles in fetal, neonatal and adult guinea pigs. Am Rev Respir Dis 146: 1192–1197
8. Rastogi A, Luayon M, Oluade AA, Pildes RS (1994) Nebulized furosemide in infants with bronchopulmonary dysplasia. J Pediatr 125: 976–979
9. Prabhu V, Keszler M, Dhanireddy R (1995) Effect of nebulized versus intravenous furosemide on pulmonary function in infants with chronic lung disease. Pediatr Res 37 (4): 346 A
10. Smith SA, Pillers DA, Gilhooly JT, Wall MA, Olsen GD (1995) Furosemide pharmacokinetics following intratracheal instillation in the guinea pig. Biol Neonate 68: 191–199
11. Raval NC, Leef KH, Antunes MJ, Stefano JL (1994) Effect of aerosolized furosemide on pulmonary function in infants with BPD: A randomized, blinded placebo-controlled trial. Pediatr Res 35: 350 A
12. Aufricht C, Votava F, Marx M, Frenzel K, Simbruner G (1995) Topically applied furosemide improves lung mechanics in infants after open heart surgery. Pediatr Res 37: 237 A
13. Karpel JP, Dworkin F, Hager D, Feliciano S, Shapiro D, Posner L, Luks D (1994) Inhaled furosemide is not effective in acute asthma. Chest 106: 1396–1400
14. Aranda JV, Perez J, Sitar DS, Collinge J, Portuguez-Malavasi A, Duffy B, Dupont C (1993) Pharmacokinetic disposition and protein binding of furosemide in newborn infants. J Pediatr 93: 507–511
15. Peterson RG, Simmons MA, Rumack BH, Levine RL, Brooks JG (1980) Pharmacology of furosemide in the premature newborn infant. J Pediatr 97: 139–143
16. Haas M (1994) The Na-K-Cl Cotransporters. Am J Physiol 267 (Cell Physiol 36): C869–C885
17. Pye S, Pavord I, Wilding P, Bennet J, Knox A, Tattersfield A (1995) A comparison of the effects of inhaled furosemide and ethacrynic acid on sodium-metabisulfite-induced bronchoconstriction in subjects with asthma. Am J Respir Crit Care Med 151: 337–339
18. Inoue T, Shigeta H, Shimizu T, Morikawa A, Suzzki W, Watanabe N, et al. (1995) Effect of inhaled furosemide on lung clearance of technetium-99m-DTPA. J Nucl Med 36: 73–77
19. Alton EWFW, Kingsleigh-Smith DJ, Munkonge FM, Smith SN, Lindsay ARG, Gruenert DC, et al. (1996) Asthma prophylaxis agents alter the function of an airway epithelial chloride channel. Am J Respir Cell Mol Biol 14: 380–387