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Faster and more reliable absorption of adrenaline by aerosol inhalation than by subcutaneous injection

H. MELLEM[1], K. LANDE[1], S. E. KJELDSEN[1], A. WESTHEIM[2], I. EIDE[1], P. F. EKHOLT[3] & N. P. BOYE[1]
Departments of [1]Internal Medicine and [2]Clinical Physiology, Ullevaal Hospital, Oslo 4 and [3]Department of Internal Medicine, Sentralsykehuset i Østfold, Fredrikstad, Norway

1 The aim of the present study was to compare absorption of adrenaline given by aerosol spray inhalation with absorption after subcutaneous injection.
2 Arterial plasma adrenaline was measured in nine healthy volunteers following adrenaline administration by both methods.
3 Following inhalation of 20 puffs of adrenaline aerosol, 0.15 mg/puff, a peak arterial adrenaline concentration after 1 min and a rapid fall to baseline from this peak occurred.
4 When given by subcutaneous injection absorption was slower with a peak arterial adrenaline concentration after 4 min. The fall in arterial adrenaline from this peak level was not statistically significant within 30 min after injection.
5 There was less intersubject variation of arterial adrenaline concentration following inhalation when compared with injection.
6 Heart rate, blood pressure and finger tremor followed the changes in arterial adrenaline concentrations.
7 These results indicate that absorption is more reliable when adrenaline is given by inhalation. The rapid fall in arterial adrenaline following inhalation, suggests that repeated inhalations are necessary when such adrenaline therapy is required.

Keywords adrenaline drug aerosol therapy anaphylaxis heart rate blood pressure finger tremor

Introduction

Adrenaline administration for emergency treatment of anaphylaxis is often recommended as subcutaneous injection, but the rate of absorption by this method is unpredictable (Barach *et al.*, 1984; Heilborn *et al.*, 1986). Rapid absorption of adrenaline from the airways after intratracheal instillation (Greenberg *et al.*, 1979; Redding *et al.*, 1967; Roberts *et al.*, 1979) or spray inhalation has been reported (Dahlof *et al.*, 1987; Davies, 1975; Heilborn *et al.*, 1986), but exact data on the rate of absorption and elimination have been lacking.

Previous studies of adrenaline absorption given by subcutaneous injection, inhalation, or as eyedrops have estimated adrenaline concentrations in peripheral venous blood (Dahlof *et al.*, 1987; Heilborn *et al.*, 1986) and urine (Hoehne *et al.*, 1970). Since arterial adrenaline levels are approximately 50% higher than peripheral venous levels due to tissue extraction and metabolism, measurement of plasma adrenaline in arterial blood allows a good estimate of systemic adrenaline level (Kjeldsen *et al.*, 1986).

When adrenaline is inhaled as an aerosol, less than 10% reaches the respiratory epithelium (Davies, 1975; Pauwels, 1985) where it seems to be absorbed rapidly. The remaining 90% or more of the spray dose is swallowed and not absorbed (Dahlof *et al.*, 1987; Heilborn *et al.*, 1986). Accordingly it can be estimated that if 3 mg adrenaline is inhaled, approximately 0.3 mg, or possibly less, reaches the respiratory epithelium. In the present study this dose was compared with the 0.5 mg given subcutaneously. Furthermore, arterial adrenaline concentrations were measured after both inhalation of adrenaline spray and subcutaneous adrenaline injection. Concomitant measurements of heart rate, blood pressure and finger tremor as clinical parameters were also performed.

Methods

Nine healthy subjects, five females and four males, aged 29 to 39 years (median 31) weighing from 51 to 97 kg (median 61) participated in the study after informed consent. The study protocol was approved by the

Correspondence: Dr H. Mellem, Department of Internal Medicine, Ullevaal Hospital, N-0407 Oslo 4, Norway

Norwegian Drug Administration (Statens legemiddelkontroll) and the hospitals Ethics committee. Each subject was aquainted with all of the investigators involved in the study. The spray inhalation technique had been demonstrated for the subjects and they had practiced spray inhalation technique before the study commenced. One subject was examined each day.

Subjects were instructed to have a light breakfast and to avoid milk, tea, coffee and tobacco overnight. The study commenced at 08.30 h by which time an intra-arterial (left brachial artery) catheter had been inserted after local lignocaine (Xylocain, Södertälje, Sweden) anaesthesia.

The volunteers were monitored by a continuous ECG recorder. Blood pressure was measured with a semi-automatic blood pressure monitor (Criticon Dinamap Vital Signs Monitor, Critikon Inc., Tampa, Fla, USA) with the cuff around the right upper arm. An acceleration transducer for measuring fingertremor was attached to the right index finger. The acceleration signals and amplitudes were registered and finger tremor was measured as described by Dietrichson *et al.* (1978).

At 08.30 h the subject started a 30 min resting period in the supine position. Sleep was not allowed. Care was taken to avoid noise and other disturbances. At 08.45 h (indicated as −15 min on the graphs) and 15 min later, measurements of heart rate, blood pressure and fingertremor were recorded and samples of arterial blood were taken. The subject then sat up and inhaled 20 puffs of adrenaline aerosol spray (Adrenaline Medihaler 0.15 mg/puff, 3M Riker, Loughborough, England) within 5 min (range 3–5 min). After inhalation of adrenaline spray, the supine postition was resumed for the rest of the study and time was reset to 0 min (Figures 1–4).

At 09.30 h (30 min on the time axis) 0.5 mg adrenaline (Adrenaline 1 mg ml^{-1}, NAF Laboratories, Oslo, Norway) was injected subcutaneously in the deltoid area of the right arm. Time points for blood sampling and recording of clinical variables are indicated in the figures.

To estimate endogenous adrenaline release caused by sitting up and hyperventilating, a pilot study was performed on three healthy 40-year-old men. The three volunteers were subjected to the same basal resting conditions and the same procedure for insertion of arterial catheters as described above. After the basal resting period the subjects sat up, hyperventilated voluntarily for 5 min and then resumed the supine resting position. Arterial blood was sampled at basal conditions, after 3 and 5 min of hyperventilation and 5 and 15 min after having stopped hyperventilation.

Plasma adrenaline was analysed with a radioenzymatic technique (Kjeldsen *et al.*, 1982; Peuler & Johnson, 1977).

Statistics

Because of the limited number of subjects included, non-parametric statistics were used. The median and 95% confidence interval were calculated according to the method of Walsh (Brown & Hollander, 1980). Friedman's test was used to evaluate the effect of the interventions. This is a non-parametric two-way analysis of variance and is analogous to parametric repeated-measures analysis of variance (Glantz, 1987). If changes during the intervention can be detected, the test includes methods for comparing all single values to one another (Conover, 1980).

Results

Arterial plasma adrenaline concentration

There was a rise in arterial adrenaline after inhalation in all subjects. The highest median concentration was reached 1 min after inhalation after which there was a gradual fall in plasma adrenaline (Figure 1). The individual peak adrenaline concentrations occurred at 1 min in all subjects. The median values at 4 min and later (until 30 min) were all significantly lower than the peak value ($P < 0.01$). Thirty minutes after inhalation plasma adrenaline was not significantly different from baseline.

The rise in plasma adrenaline was slower after subcutaneous administration than inhalation. Maximum median adrenaline concentration was observed 4 min after injection. The individual peak adrenaline concentrations occurred 4 min after injection in all subjects but two whose peak occurred 30 min after injection. The gradual fall from the maximum median concentration did not reach statistical significance. Whilst plasma concentrations of adrenaline were decreasing 2 min after inhalation, they were still increasing 2 min after injection.

The peak median concentration of plasma adrenaline after inhalation was not significantly different from the peak median concentration after injection.

Estimated median adrenaline concentrations after injection showed more variability (expressed as 95% confidence intervals in Figure 1) compared with values measured after inhalation.

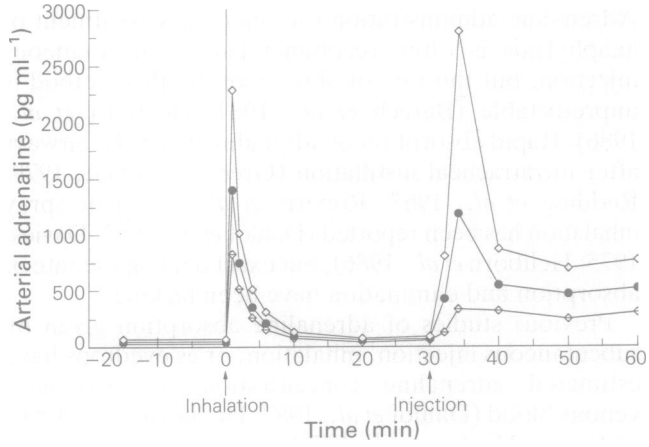

Figure 1 Arterial adrenaline concentrations before and after inhalation and subcutaneous injection.
• Median adrenaline concentration
◇ Upper limit 95% confidence interval
◈ Lower limit 95% confidence interval
0 time values represent resting conditions immediately before start of spray inhalation.
1 min values represent values 1 min after inhalation of spray had stopped. 30 min values represent values immediately before s.c. injection.

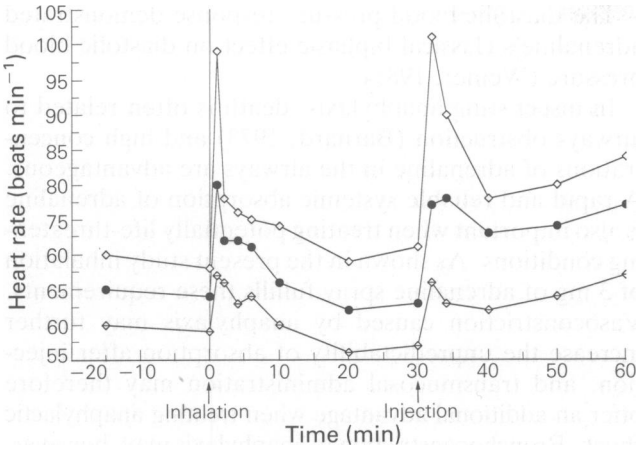

Figure 2 Heart rate before and after inhalation and subcutaneous injection of adrenaline.
• Median heart rate
◇ Upper limit 95% confidence interval
◈ Lower limit 95% confidence interval
Timing of events as explained in Figure 1.

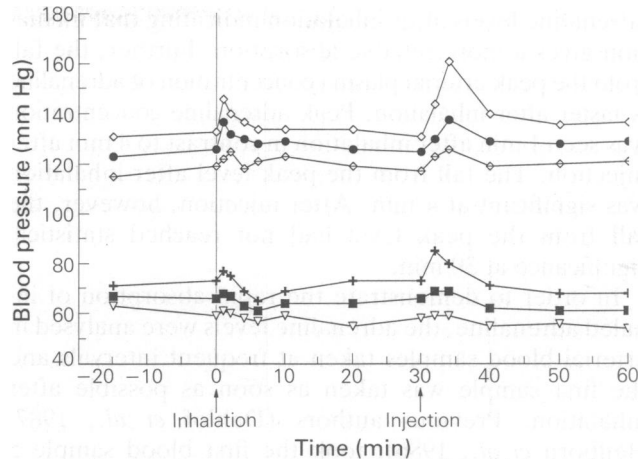

Figure 3 Variation in blood pressure before and after inhalation and subcutaneous injection of adrenaline.
• Median systolic blood pressure
◇ Upper limit 95% confidence interval
◈ Lower limit 95% confidence interval
■ Median diastolic blood pressure
+ Upper limit 95% confidence interval
▽ Lower limit 95% confidence interval
Timing of events as explained in Figure 1.

In the pilot study arterial plasma adrenaline did not rise as a consequence of sitting up and hyperventilating and never exceeded 120 pg ml^{-1}. The degree of hyperventilation was indicated by an increase of mean arterial pH from 7.4 before, to 7.69 immediately after hyperventilation and a fall of mean pCO_2, from 5.54 kPa to 3.34 kPa.

Heart rate

Heart rate increased to a maximum level 1 min after inhalation ($P < 0.01$) and then fell gradually to levels not significantly different from baseline at 10, 20 and 30 min after inhalation (Figure 2). Heart rate increased to a peak 2 min after the injection ($P < 0.01$) but the slight fall after this time-point was not significantly different from the peak level. Thus after injection peak heart rate on average occurred 2 min before peak plasma adrenaline concentration and persisted without any significant fall throughout the study period.

Blood pressure

Although not statistically significant, the change in systolic blood pressure followed the same trend as the change in arterial plasma adrenaline concentration (Figure 3). There was an initial rise in diastolic blood pressure following both injection and inhalation but these changes were not statistically significant. Diastolic blood pressure, however, fell significantly from baseline 6 min after inhalation and 20 min after injection ($P < 0.05$).

Finger tremor

Finger tremor increased significantly 2 min after inhalation and 4 min after injection (Figure 4). Peak finger tremor after inhalation was significantly higher than the peak after injection ($P < 0.01$). While finger tremor decreased gradually from its peak value after inhalation, there was no significant fall from the peak level after injection.

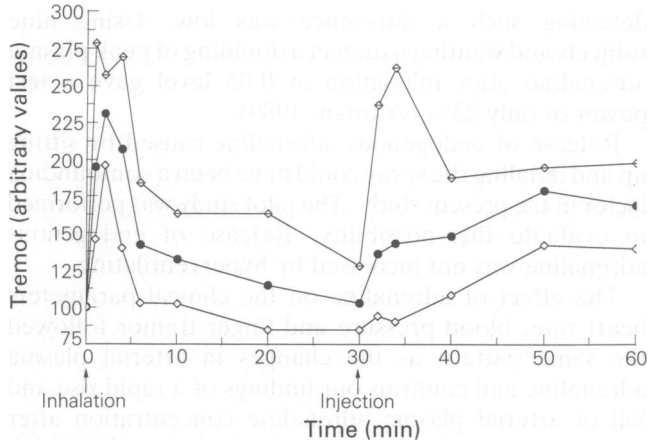

Figure 4 Variation in finger tremor before and after inhalation and subcutaneous injection of adrenaline.
• Median finger tremor
◇ Upper limit 95% confidence interval
◈ Lower limit 95% confidence interval
Timing of events as explained in Figure 1.

Adverse effects

None of the subjects reported gastrointestinal symptoms in connection with the study. Slight pain and tenderness where the arterial catheter had been inserted was reported by some of the subjects for up to 2 weeks after the study.

Discussion

The results indicate that inhalation gives a faster absorption of adrenaline than subcutaneous injection. There is also less intersubject variation in plasma

adrenaline levels after inhalation indicating that inhalation gives a more reliable absorption. Further, the fall from the peak arterial plasma concentration of adrenaline is faster after inhalation. Peak adrenaline concentration was seen 1 min after inhalation in contrast to 4 min after injection. The fall from the peak level after inhalation was significant at 4 min. After injection, however, the fall from the peak level had not reached statistical significance at 30 min.

In order to demonstrate the rapid absorption of inhaled adrenaline, the adrenaline levels were analysed in arterial blood samples taken at frequent intervals and the first sample was taken as soon as possible after inhalation. Previous authors (Dahlof *et al.*, 1987; Heilborn *et al.*, 1986), took the first blood sample 5 min after inhalation when measuring venous plasma adrenaline and thus described a different profile of the rate of absorption of inhaled adrenaline than has been found in this study.

The doses of 3 mg inhaled adrenaline and of 0.5 mg injected adrenaline are not equivalent, but seem appropriate for the purpose of demonstrating the rate and reliability of absorption of adrenaline. The peak concentrations found by the two methods of administration were not significantly different. Because of a considerable variation in peak values between subjects, test power for detecting such a difference was low. Using nine subjects and wanting to detect a doubling of peak plasma adrenaline after inhalation at 0.05 level gave a test power of only 23% (Altman, 1980).

Release of endogenous adrenaline caused by sitting up and inhaling the spray could have been a confounding factor in the present study. The pilot study was performed to evaluate this possibility. Release of endogenous adrenaline was not increased by hyperventilating.

The effect of adrenaline on the clinical parameters heart rate, blood pressure and finger tremor followed the same pattern as the changes in arterial plasma adrenaline and confirms our findings of a rapid rise and fall of arterial plasma adrenaline concentration after inhalation, a slower absorption with a sustained high plasma adrenaline concentration after injection, and a greater intersubject variation after injection compared with inhalation.

The diastolic blood pressure response demonstrated adrenaline's classical biphasic effect on diastolic blood pressure (Weiner, 1985).

In insect sting anaphylaxis, death is often related to airways obstruction (Barnard, 1973) and high concentrations of adrenaline in the airways are advantageous. A rapid and reliable systemic absorption of adrenaline is also important when treating potentially life-threatening conditions. As shown in the present study inhalation of 3 mg of adrenaline spray fulfills these requirements. Vasoconstriction caused by anaphylaxis may further increase the unpredictability of absorption after injection, and transmucosal administration may therefore offer an additional advantage when treating anaphylactic shock. Bronchoconstriction in anaphylaxis may, however, obstruct the availability of inhaled adrenaline.

The rapid fall of plasma adrenaline from the peak level after inhalation may require repeated inhalations when treating e.g. anaphylaxis. A more potent adrenaline aerosol spray than what is available at present should be developed since as many as 20 inhalations are unpractical and may cause symptoms of hyperventilation.

Intramuscular injection of adrenaline is often recommended for treatment of anaphylaxis. Studies comparing the bioavailability of adrenaline after intramuscular injection and the other routes of administration are needed.

The higher concentrations of adrenaline found in arterial than venous blood are advantageous when studying systemic adrenaline levels. Arterial sampling is, however, more invasive than sampling of venous or arterialised venous blood which would probably be adequate for studies on the bioavailability of adrenaline given by different routes of administration.

In conclusion, inhaled adrenaline shows more rapid and reliable absorption than subcutaneous injection. Repeated inhalations of adrenaline spray may be an adequate method for self-treatment with adrenaline.

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