Short reports

Actions of salbutamol, disodium cromoglycate, and placebo administered as aerosols in acute asthma

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SUMMARY The effects on the peak expiratory flow rate of the drug sequences, placebo-salbutamol-disodium cromoglycate and placebo-disodium cromoglycate-salbutamol administered via a nebuliser were examined in 35 children with asthma. Twenty children were each examined once within 4 hours of admission to hospital with an acute attack of asthma, and the remaining 15 children were examined later in the attack on two occasions. The placebo effect of sterile water accounted for about half of the total bronchodilator action both early and late in the attack. It is suggested that this effect is due to the action of water on the surface film of surfactant, causing collapse of bubbles and strands or webs of mucoid material, thus decreasing airways resistance. At this time salbutamol is significantly more potent than disodium cromoglycate as a bronchodilator agent.

Salbutamol and disodium cromoglycate (DSCG) play an important part in the management of the acute attack of asthma. It was shown that each has bronchodilator properties in children with asthma if the children are examined at a time when they are well and have no recent history of an attack.¹ This result was surprising, as DSCG has not been regarded as a powerful bronchodilator comparable with beta-2 stimulants. Also, it was noted in this study that the placebo effect due to inhaled water was small, 1% of the initial value.

The clinical impression is firmly established that in an asthmatic attack salbutamol continues to be an effective bronchodilator, but DSCG is generally regarded as ineffective at such time. Comparisons between intravenous and inhaled salbutamol have shown equal effectiveness of action.² There is a difference of opinion however on this point,^{3,4} and diminished effectiveness of inhaled salbutamol would accord with the firm clinical impression that in very

severe asthma beta-2 stimulants become less effective. Little is known about the relative actions of placebo in the acute attack and between attacks.

In this study the actions were compared of inhaled salbutamol, inhaled DSCG, and placebo, early and late, in an acute attack of asthma.

Methods

The 35 children studied were admitted with an acute attack of asthma. Fifteen were examined on two occasions late in the attack, and 20 were examined on one occasion early in the attack.

Fifteen were examined the following morning, 12-24 hours after admission and again the next day. On the first occasion alternate patients received the drug regimen: placebo (sterile water for injections BP) 2 ml given after measurement of the initial peak expiratory flow rate (PEFR), followed 30 minutes later by salbutamol 5 mg in 2 ml of solution, and 60 minutes later by DSCG 20 mg in 2 ml of solution. Alternate patients received the drugs in the reverse sequence, placebo-DSCG-salbutamol. Preliminary observations had shown that the placebo effect was complete at about 30 minutes, but it is possible that water in the DSCG + salbutamol preparations could have contributed to apparent drug effects, but this does not invalidate the comparison between the drugs. PEFR measurements were repeated at 5-minute intervals throughout the study, and values at 30, 60, and 90 minutes, when maximum effects for each treatment had been reached, were used for statistical analysis. The same children were examined 24 hours later by the alternative drug sequence. A child was eliminated from the study and not given the second sequence if the PEFR failed to be within $\pm 10\%$ of the value on the first day. In this way the children chosen were ones in whom recovery was prolonged and the clinical state was fairly stable. None of these children was breathless at rest or had tachypnoea, but there was wheeze, and rhonchi were

audible over the lung fields. Bronchodilator drugs were avoided for 6 hours before the study. The doctors carrying out the study were not part of the team managing the patient; the patient's doctor was free to make any decision regarding treatment he considered necessary for the child. Consent from parents and approval of the ethical committee was obtained for this and the following protocol. The 15 children were aged 5½ to 15 years (mean 11·3) and had a long history of asthma. All except the 2 youngest had positive skin tests to one of the common allergens. All had received DSCG as part of maintenance treatment and 3 had been on beclomethasone. Some had received steroids, but not within 2 months of the start of the study.

The examination of the same patients by alternate drug sequences had advantages, but meant that those examined had suffered fairly mild attacks and this, plus examination fairly late in the attack, might have led to loss of important information, especially as clinical observation suggests that resistance to bronchodilator drugs occurs in severe asthma. Therefore, 10 children admitted with an acute attack were examined by the drug sequence placebo-salbutamol-DSCG within 4 hours of admission, and a further 10 of comparable age, sex, and history of asthma were examined by the drug sequence placebo-DSCG-salbutamol. Any child in whom the severity of attack was such that the PEFR could not be reliably measured was excluded, as was any child who was judged by his own doctor to need

steroids as initial treatment. All children had tachypnoea or dyspnoea (or both), wheeze, and rhonchi. The PaCO_2 was not raised in those in whom the admitting team requested measurement because of the severity of attack. Oxygen was given as indicated. The 20 subjects were aged 7-14 years (mean 10½). Seventeen had positive skin tests and all had had asthma for at least one year. Fifteen were on regular DSCG powder and 4 were on beclomethasone. Treatment before and after admission was documented in order to ensure that it did not differ significantly in the two groups of 10 subjects.

Results

Tables 1 and 2, and the Figure, show the increments in PEFR and significance levels in response to placebo and the two drug sequences. In the group of 15 children examined by the sequence placebo-salbutamol-DSCG and then placebo-DSCG-salbutamol, the response to placebo was 16·9 and 15·6% of predicted normal (34 and 28% of the initial values) respectively, a difference which is not significant (Figure and Table 1). The subsequent response to salbutamol was 9·8% of predicted (19% of the initial value) and to DSCG 4·3% of predicted (8% of the initial value), a difference which just fails to achieve significance at $P = 0·05$.

After the administration of the second drug in each case, combined drug effects were 15·2 and 12·7% of predicted, a difference which is not

Table 1 Mean values for PEFR in response to placebo and drugs in 15 children examined late in an acute attack of asthma

Placebo-salbutamol-cromoglycate sequence				Placebo-cromoglycate-salbutamol sequence			
Predicted normal	339 ± 94	$P < 0·001$ $P < 0·001$ $P < 0·001$ $0·05 > P > 0·02$		Predicted normal	339 ± 94	$P < 0·001$ $P < 0·001$ $P < 0·001$ $P < 0·001$	
Initial PEFR	183 ± 71			Initial PEFR	208 ± 82		
After placebo	240 ± 90			After placebo	259 ± 96		
After salbutamol	271 ± 93			After DSCG	275 ± 101		
After DSCG	295 ± 90			After salbutamol	298 ± 91		

Table 2 Mean values for PEFR in response to placebo and drugs in two groups of 10 children examined early in an acute attack of asthma

Placebo-salbutamol-cromoglycate				Placebo-cromoglycate-salbutamol			
Predicted normal	310 ± 59	$P < 0·001$ $P < 0·001$ $P < 0·001$ $P > 0·1$		Predicted normal	275 ± 64	$P < 0·001$ $0·01 > P > 0·002$ $0·1 > P > 0·05$ $0·01 > P > 0·002$	
Initial PEFR	135 ± 39			Initial PEFR	113 ± 70		
After placebo	177 ± 56			After placebo	157 ± 76		
After salbutamol	229 ± 60			After DSCG	171 ± 85		
After salbutamol + DSCG	226 ± 58			After DSCG + salbutamol	215 ± 91

Figure 1 *I* = values before drugs; *P* = changes after placebo; *S* = changes after salbutamol; *G* = changes after DSCG; *S*+*G*, *G*+*S*, changes after salbutamol followed by DSCG, and DSCG followed by salbutamol respectively; *S*₁, 10 subjects examined early in attack by drug sequence placebo–salbutamol–DSCG; *S*₂, 10 different subjects examined early in attack by drug sequence placebo–DSCG–salbutamol; *S*₃, 15 subjects examined late in attack by drug sequence placebo–salbutamol–DSCG; *S*₄, the same 15 subjects examined late in attack by the drug sequence placebo–DSCG–salbutamol.

significant. Therefore, although from the Figure salbutamol appears to be more effective in terms of mean values than DSCG, the difference is not significant.

In the two groups of 10 children, each examined early in the attack shortly after admission, certain differences become apparent (Table 2). Placebo effects were 13.2 and 17.2% of predicted (31 and 55% of the initial values), a difference which is not significant. The subsequent response to salbutamol was 17.4% of predicted (42% of the initial value), and to DSCG 4.5% (12% of the initial value), a difference which is highly significant ($0.01 > P > 0.002$). After the administration of the second drug, the combined drug effects were 16.9 and 20.9% of predicted, a difference which is not significant.

Discussion

The results reported here and elsewhere¹ show that the actions of placebo, salbutamol, and DSCG vary considerably with the state of the asthma. It was noted by Chung and Jones¹ that in the phase between attacks the placebo effect was quite small, a mean increase of 2.5 litres, relative to the drug effects, and that the bronchodilator actions of salbutamol and DSCG were about equal (54 and 50 litres respectively), both being powerful bronchodilators. The mean predicted normal in that study was 305.9 litres. By contrast the placebo effects in the present study are 57 and 51 litres compared with salbutamol and DSCG effects of 31 and 16 litres, late in the attack (Table 1). Early in the attack, the figures are placebo effects 42 and 44 litres against drug effects of 52 and 14 litres (Table 2). The placebo effect during an attack is much greater both absolutely and in comparison with the drug effects, and this is true both early and late in the attack. It causes about one-half of the total bronchodilator effect. Most of the drug effect is due to salbutamol, especially early in the attack. There is no suggestion that one drug reinforces the action of the other and, indeed, early in the attack DSCG appears to detract slightly from the action of salbutamol. There seems no point therefore, in using DSCG in addition to salbutamol during the acute attack.

The placebo effect occurs rapidly, it is large in relation to the drug effects, and is present at a time when the airway is full of mucoid secretion, which would be expected to produce a fairly fixed increase in airways resistance. It contains bubbles and strands or webs of mucoid material across the airways which produce the auscultatory features of an attack. It is suggested that the nebulised particles of water act by altering the properties of the surface film, causing collapse of bubbles, strands or webs, thereby decreasing resistance. Water rapidly counteracts the action of surfactant by 'drowning' the phospholipid radicles. Cough is a prominent feature of the acute attack and bubbles generated by coughing must contribute considerably to the total volume of secretion and hence to the degree of obstruction. Moreover, it is well known that a fit of coughing increases resistance and this may well be due in part to bubble and strand, or web formation. A calm, supportive attendant who encourages quiet regular, cough-free breathing while the patient inhales humidified oxygen often produces improvement which is assumed to be evidence of a psychological effect. This must be questioned, as indeed must the rationale in general of humidification as a method of treatment. The fairly small amount of water administered and the rapidity of action are against any effect on viscosity.

Resistance to DSCG in acute asthma is greater therefore, than to salbutamol. However, clinical observation suggests that resistance to beta-2 stimulants does also increase with severity of the attack. It would appear probable that only when severity exceeds the point at which measurements can be made with a peak flow meter does resistance to salbutamol become pronounced. Although placebo effects are greater in the attack than between attacks, again no information is available about attacks severe enough to prevent measurement using a peak flow meter.

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References

- 1 Chung J T N, Jones R S. Bronchodilator effect of sodium cromoglycate and its clinical implications. *Br Med J* 1979; **ii**: 1033-4.
- 2 Lawford P, Jones B J M, Milledge J S. Comparison of intravenous and nebulised salbutamol in initial treatment of severe asthma. *Br Med J* 1978; **i**: 84.
- 3 Anonymous. Intravenous versus inhaled salbutamol. *Lancet* 1978; **i**: 80.
- 4 Williams S, Seaton A. Intravenous or inhaled salbutamol in severe acute asthma. *Thorax* 1977; **32**: 555-8.

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The steatocrit: a simple method for estimating stool fat content in newborn infants

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SUMMARY A simple micromethod is described for estimating the stool fat content of newborn babies. It is quick and reliable, requires only a small amount of stool, and can be used as a screening test for newborn babies suspected of fat malabsorption.

Many infants, especially those of low birthweight or short gestation, gain weight slowly in the early neonatal period. There are many reasons for such poor weight gain among which the loss of excess dietary fat in the stools needs to be considered. We have previously shown that it is possible to use a very simple method based on microcentrifugation for predicting the fat content and caloric value of milk.¹ In this study we have investigated the application of microcentrifugation to newborn infants' stool samples to measure stool fat content.

Method

Water content of the stool. In order to express the stool fat per gram wet weight of stool, it was first necessary to ensure that the water content of the stool was not in itself an important variable. Ten samples of stool from 3 term and 7 preterm infants,

6 fed on expressed breast milk and 4 on a milk formula, were weighed wet and then freeze dried for 24 hours and reweighed. The water content of the stool was thus estimated and expressed as a percentage of the wet weight.

Stool fat measurement. Stools were weighed and homogenised with a small amount of sand (0.06 g) and two volumes of water, using a pestle and mortar and a hand homogeniser. Small amounts of well homogenised stool (about 75 μ l) were drawn by a pipette into a capillary tube (for this technique blood pH capillary tubes cut to the same length as standard glass capillary tubes were used). They were sealed at one end by a flame and centrifuged for 15 minutes at 12 000 g, using a haematocrit centrifuge (Hawksley, London).

After centrifugation the tubes were removed immediately and placed vertically. The length of the fat layer at the top and that of the solid layer at the bottom was measured with vernier callipers to the nearest 0.05 mm. Stool fat content was expressed as a percentage (steatocrit) of the total length of the *solid* column in the tube (that is fat layer + solid layer) (Fig. 1). The steatocrit was measured in duplicate. The stool fat content was also measured by Sobel's method² which requires 3 g of stool.