

be assumed not to be, planning a pregnancy. A treatment which minimised the likelihood of a delayed bleed, and therefore the requirement for a pregnancy test, would seem advantageous. The three pregnancies conceived after mifepristone treatment suggests that the next cycle and ovulation may occur without an intervening bleed. As we found no true failures of mifepristone treatment it would seem reasonable to start hormonal contraception immediately after treatment. This would give good protection against unplanned pregnancy and obviate the need for pregnancy testing unless the withdrawal bleed after the first cycle of treatment is absent.

### Conclusions

Most abortions in the Western World are carried out in young women, often early on in their sexual relationships. Knowledge and availability of postcoital contraception can reduce the numbers of unplanned pregnancies and give health professionals the opportunity to encourage and supply ongoing effective contraception.

We have shown that the mifepristone and Yuzpe regimens are effective. Mifepristone has greater effectiveness and fewer side effects but leads to greater disturbance of cycle and to difficulty in predicting risk of pregnancy until the following cycle. The Yuzpe method seems to be slightly less effective and has more side effects but rarely delays the next cycle. Danazol did not seem to be effective as postcoital contraception. The risk of pregnancy for each woman can be estimated reasonably accurately by careful questioning regarding the stage of the cycle and measurement of progesterone. To determine the relative usefulness and practical effectiveness of the Yuzpe and mifepristone regimens in clinical practice we suggest a large multicentre study including all women requiring postcoital contraception, even if their level of risk is difficult to determine.

This study was funded by the special programme of research, development, and research training in human reproduction of the World Health Organisation. We thank

Brian Faragher for help with statistical analysis, Jacky Vance for persistence in achieving follow up, and Rosemary Kirkman for support and advice.

- 1 Haspels AA. Interception: post-coital estrogens in 3016 women. *Contraception* 1976;14:375-81.
- 2 Dixon GW, Schlesselman JJ, Ory HW, Blye RP. Ethinylestradiol and conjugated estrogens as postcoital contraceptives. *JAMA* 1980;244:1336-9.
- 3 Yuzpe AA, Smith RP, Rademaker AW. A multicentre clinical investigation employing ethinylestradiol combined with dl-norgestrel as a postcoital contraceptive agent. *Fertil Steril* 1982;37:508.
- 4 Percival-Smith RK, Abercrombie B. Postcoital contraception with dl-norgestrel/ethinylestradiol combination: six years' experience in a student medical clinic. *Contraception* 1987;36:287-93.
- 5 Van Santen MR, Haspels AA. A comparison of high dose estrogen versus low dose ethinylestradiol and norgestrel combination in post coital interception: a study in 493 women. *Fertil Steril* 1985;43:206-13.
- 6 Tietze C. Probability of pregnancy resulting from a single unprotected coitus. *Fertil Steril* 1960;11:485-8.
- 7 Barret JC, Marshall J. The risk of conception on different days of the menstrual cycle. *Population Studies* 1969;23:455-61.
- 8 Vollman RF. Assessment of the fertile and sterile phases of the menstrual cycle. *International Review of Natural Family Planning* 1977;1:40-7.
- 9 Schwartz D, Mayoux MJ, Martin-Boyce A, Czyglik F, David G. Donor insemination: conception rate according to cycle day in a series of 821 cycles with a single insemination. *Fertil Steril* 1979;31:226-9.
- 10 Department of Health. *Handbook of contraceptive practice*. London: DoH, 1990.
- 11 Rowlands S, Guillebaud J, Bounds W, Booth M. Side effects of danazol compared with an ethinylestradiol/norgestrel combination when used for postcoital contraception. *Contraception* 1983;27:39-49.
- 12 Zuliani G, Colombo UF, Molla R. Hormonal postcoital contraception with an ethinylestradiol norgestrel combination and two danazol regimens. *Eur J Obstet Gynecol Reprod Biol* 1990;37:253-60.
- 13 Van Santen MR, Haspels AA. Interception III: postcoital luteal contraception by an antiprogesterin (mifepristone, RU486) in 62 women. *Contraception* 1987;35:423-32.
- 14 Van Santen MR, Haspels AA. Interception IV: failure of mifepristone (RU486) as a monthly contraceptive, "Lunarette." *Contraception* 1987;35:433-8.
- 15 Lähteenmäki P, Rapeli T, Käriäinen M, Alftan H, Ylikorkala O. Late postcoital treatment against pregnancy with antiprogesterone RU486. *Fertil Steril* 1988;50:36-8.
- 16 Nadler RD, Roth-Meyer C, Baulieu EE. Behavioral and endocrine consequences of long-term antiprogesterone (RU486) administration to Cynomolgus monkeys: preliminary results. In: Baulieu EE, Segal SJ, eds. *The antiprogesterin steroid RU486 and human fertility control*. New York: Plenum Press, 1985:169-77.
- 17 Hermann WL, Schindler AM, Wyss R, Bischof P. Effects of the antiprogesterone RU486 in early pregnancy and during the menstrual cycle. In: Baulieu EE, Segal SJ, eds. *The antiprogesterin steroid RU486 and human fertility control*. New York: Plenum Press, 1985:199-209.
- 18 Fasoli M, Parazzini F, Cecchetti G, Lavecchia C. Postcoital contraception: an overview of published studies. *Contraception* 1989;39:459-68.
- 19 Gardner MJ, Altman DG. *Statistics with confidence*. London: British Medical Journal, 1989.
- 20 Dhont M, Thierry M, Vandekerckhove D. Human chorionic gonadotrophin (HCG) assay in the diagnosis and management of early pregnancy disorders. *J Obstet Gynecol* 1982;2:134-9.

(Accepted 3 September 1992)

## Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaler

James R W Wilkinson, J Alan Roberts, Peter Bradding, Stephen T Holgate, Peter H Howarth

Salmeterol is a long acting  $\beta_2$  agonist used as a bronchodilator in asthma. Patients have been reported as suffering acute deteriorations in their asthma, often within minutes of exposure to salmeterol and against a background of stable asthma.<sup>1</sup> We report six cases of acute bronchospasm induced by inhaling salmeterol by metered dose inhaler but not by dry powder inhaler (diskhaler).

### Patients, methods, and results

Five female and one male asthmatic patient (aged 17-48 years, mean 28) complained of breathlessness, wheeze, or cough after inhaling salmeterol. All subjects were taking inhaled salbutamol as necessary; five were taking regular beclomethasone, and one additional

prednisolone. One subject took regular salmeterol (by diskhaler), one oral salbutamol, and one oral theophylline. Forced expiratory volume in one second at rest ranged from 69% to 105% of predicted values for age, sex, and height.

All subjects attended on three occasions, when they received two puffs of salmeterol or placebo by metered dose inhaler given double blind and in random order or salmeterol 50  $\mu$ g by diskhaler. On two further visits four subjects received beclomethasone (Becotide) 100  $\mu$ g and three salbutamol (Ventolin) 200  $\mu$ g (given double blind in random order) (see figure). Intervals between treatments were 2-14 days. All subjects abstained from taking salmeterol for 24 hours and salbutamol for six hours before challenge. Forced expiratory volume in one second was measured before and at one, three, five, 10, 15, and 30 minutes after exposure.

Maximal percentage fall in forced expiratory volume in one second relative to baseline values was compared between treatments using Student's *t* test for paired samples.

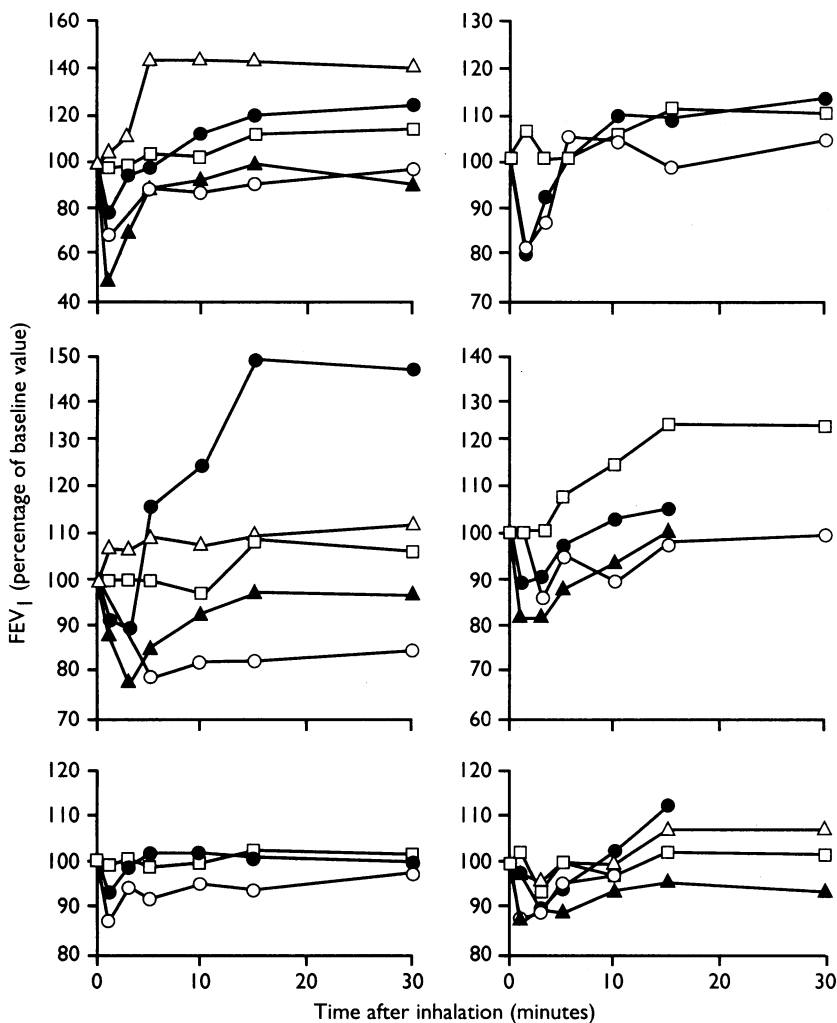
The figure shows the changes in forced expiratory volume in one second after the different treatments. In all subjects forced expiratory volume in one second fell substantially after inhalation of either salmeterol (13.2% (SE 2.5%),  $p=0.005$ ) or placebo (19.0% (3.2%),  $p=0.015$ ) by metered dose inhaler. Two

Department of Medicine 1,  
Southampton General  
Hospital, Southampton  
SO9 4XY

James R W Wilkinson,  
registrar  
J Alan Roberts, senior  
registrar  
Peter Bradding, research  
fellow  
Stephen T Holgate, MRC  
professor of  
immunopharmacology  
Peter H Howarth, senior  
lecturer in medicine

Correspondence to:  
Dr Wilkinson.

BMJ 1992;305:931-2



Changes in forced expiratory volume in one second ( $FEV_1$ ) in six asthmatic patients after inhaling salmeterol by diskhaler ( $\square$ ) and after inhaling salmeterol ( $\bullet$ ), placebo ( $\circ$ ), salbutamol ( $\Delta$ ), and beclomethasone ( $\blacktriangle$ ) by metered dose inhaler

subjects became severely wheezy, others experiencing cough and mild wheezing. There was no bronchoconstriction after salmeterol by diskhaler (1.2% (0.6%),  $p=0.14$ ). Differences between treatments were significant ( $p=0.005$  for salmeterol by metered dose inhaler *v* salmeterol by diskhaler;  $p=0.001$  for placebo by metered dose inhaler *v* salmeterol by diskhaler;  $n=6$ ).

The initial bronchoconstriction after salmeterol by metered dose inhaler resolved within five minutes,

with subsequent bronchodilation, whereas that after placebo persisted for more than 30 minutes.

Becotide induced bronchoconstriction similar to that occurring after placebo (maximal fall in forced expiratory volume in one second 26.5% (8.7%),  $p=0.001$ ;  $n=4$ ). Ventolin induced no bronchoconstriction (lowest forced expiratory volume in one second 101.7% (3.2%) of baseline values;  $n=3$ ).

Another six asthmatic patients not complaining of cough after salmeterol showed no bronchoconstriction when salmeterol was given by metered dose inhaler.

#### Comment

Bronchoconstriction after both salmeterol and placebo by metered dose inhaler but not after salmeterol by diskhaler suggests that the irritant is not the salmeterol itself. Salmeterol metered dose inhalers contain lecithin and the propellants dichlorofluoromethane and trichlorofluoromethane. Salbutamol and beclomethasone metered dose inhalers contain the same propellants but oleic acid instead of lecithin. The similarity in characteristics of bronchoconstriction after beclomethasone by metered dose inhalers implicates one or both chlorofluorocarbons rather than lecithin as the irritant. That salbutamol caused no bronchoconstriction was attributed to its faster onset of action opposing any bronchoconstrictor effects of the propellants.

Paradoxical bronchoconstriction after inhalation by metered dose inhaler has been reported with both inhaled corticosteroids and  $\beta_2$  agonists,<sup>2-4</sup> decreases in forced expiratory volume in one second of more than 10% occurring in as many as 4.4% of subjects.<sup>5</sup> Maximum bronchoconstriction occurs within five minutes but may persist for more than 30 minutes.<sup>5</sup> Salmeterol's slower onset of action may expose such bronchoconstriction in asthmatic subjects, whereas bronchodilators with a faster onset of action may attenuate the bronchoconstriction.

Such paradoxical bronchoconstriction might explain the reported worsening of asthma symptoms after inhalation of salmeterol, and we suggest that affected patients transfer to a dry powder formulation.

- 1 Committee on Safety of Medicines. *Current Problems* No 31, June 1991.
- 2 Bryant DH, Pepys J. Bronchial reactions to aerosol inhalant vehicle. *BMJ* 1976;i:1319-20.
- 3 Reisman RE. Asthma induced by adrenergic aerosols. *J Allergy* 1970;46:162.
- 4 Nicklas RA. Paradoxical bronchospasm associated with the use of inhaled beta agonists. *J Allergy Clin Immunol* 1990;85:959-64.
- 5 Yarbrough J, Mansfield L, Ting S. Metered dose inhaler induced bronchospasm in asthmatic patients. *Ann Allergy* 1985;55:25-7.

(Accepted 20 August 1992)

## ONE HUNDRED YEARS AGO

### THE ADVANTAGES OF EPIDEMICS

Out of evil comes good. A sharp epidemic, especially if fatal in type, may save many lives in the long run by educating those individuals and corporations whose obtuseness prevents them from learning in a less expensive school than that of direct experience. The dread of cholera is spurring to action many authorities who would otherwise have remained content with polluted water supplies and reeking nuisances which custom had made familiar. Small-pox, too, has been teaching many bitter lessons as to the need for means of isolation being in readiness beforehand. Now scarlet fever is enforcing the same moral, and if the lay press may be taken as an index of public opinion, there is a growing disposition to use plain language concerning sanitary authorities who fail in their duty in this matter. It is in the power of the public as ratepayers to insist upon proper means being adopted for

their safety, and the sooner the public realise the danger of delay the better. Brighthouse, for example, has learned the lesson at a cost of several lives and probably several thousands of pounds. A few of the adjoining districts have had the wisdom to profit by their neighbour's fate, and are bestirring themselves, but most are perversely content to wait as Brighthouse and Batley did until it is too late. At Golcar a case of small-pox has occurred among a colony of navvies, and has had to be left there, the sanitary authority having made no provision whatever. An outbreak of scarlet fever among Irish harvestmen at Kirkby, near Liverpool, found the rural authority equally unprepared; and although provision is now being hurriedly made, the *Liverpool Post* comments with just severity upon the previous inaction of the Board. The condemnation should have been extended to the scores of other defaulters whose inaction is no less culpable. (*BMJ* 1892;ii:599.)