

Criticism that PPA is used alone as a street drug instead of amphetamines to produce psychic stimulation is not supported by emergency room data. These data show that street-purchased "pseudo-speed" frequently consists of combinations with caffeine and ephedrine. This "pseudo-speed", coupled with alcohol and marijuana, accounts for most emergency room visits.⁴ To prevent street drug sales, it would appear to be necessary to class all of these substances as controlled drugs. Alone, PPA is devoid of abuse potential⁵ and central excitement effects.⁶ Emergency room records in the United States reveal that when over-the-counter preparations of PPA plus other drugs are involved, most patients have overdosed with suicidal intent.

Our clinical studies, on over four hundred obese patients, in which recommended dosage levels were given (25 mg three times daily or 50 mg to 75 mg sustained release) indicate that PPA is safe. These data have been submitted to the Food and Drug Administration and will be published later this year. Our own experience apart, over-the-counter advisory panels on cough/cold preparations and diet aids have, in their recommendations to the F.D.A., concluded that PPA is safe.

Contrary to the opinion expressed in your editorial, we believe a balanced evaluation of available clinical data and many years of successful use demonstrate that PPA is a safe and effective drug when used as recommended.

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SPUTUM VISCOSITY AND LONG-TERM IPRATROPIUM BROMIDE NEBULISER THERAPY

SIR,—Recently a nebuliser solution of ipratropium bromide has been released for the treatment of patients with "reversible airways obstruction", a diagnostic grouping which includes all patients with asthma and some with chronic bronchitis. The recommended dose for adults is 0.1–0.5 mg up to four times daily. The 'Atrovent' nebuliser solution data sheet states that there is no evidence that the drug in therapeutic doses adversely affects bronchial secretion, although "some patients may complain of a dry mouth". The atrovent inhaler, which has been available for several years, has proved to be of benefit in chronic obstructive bronchitis, and most cautious clinicians restrict their use of ipratropium bromide to these patients, even though the drug can be effective in the short-term management of asthma.¹ However, there is no convincing evidence that it has any advantages over beta₂-receptor agonists. Long-term management of asthma with ipratropium bromide carries the danger of increasing sputum viscosity—a highly undesirable complication in a disease in which severe attacks are characterised by mucus plugging of the bronchi. Unfortunately, the effects on sputum viscosity of long-term treatment with ipratropium bromide at the doses recommended by nebuliser have not been studied in clinical trials despite the data sheet's declaration that there is no evidence of any adverse effect.

I would expect an anticholinergic drug which can cause dry mouth in some patients to have a sputum drying effect. If this is so it should be avoided in all patients with bronchial asthma, especially in high doses by nebuliser. An asthmatic may have little regard for recommended doses when his disease is out of control: if he uses more than the recommended dose of a beta₂-agonist he will do no harm, providing he also seeks medical advice during a severe episode, but overuse of a drug which may increase sputum viscosity could have serious consequences.

Only adults with poorly controlled severe chronic asthma are considered for home nebuliser treatment. The risk is that they will delay seeking medical advice in a severe attack if they have too much

confidence in these devices. Nebulisers containing ipratropium bromide could be even more dangerous.

Ipratropium bromide in nebuliser solution is unlikely to be more beneficial than conventional pressurised aerosols in patients with chronic bronchitis and could be dangerous if used long-term in chronic asthma. I am surprised that this drug has been released without evidence that long-term treatment of patients with asthma does not adversely affect sputum viscosity.

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PROTAMINE AS A CAUSE OF GENERALISED ALLERGIC REACTIONS TO NPH INSULIN

SIR,—Allergic reactions to insulin may be due to insulin itself or to contaminants, preservatives, or other constituents of insulin preparations. Shore et al. in 1975 described a patient allergic to NPH insulin in whom the hypersensitivity was thought to be due to protamine, although this was not proved.¹ We have seen a patient with symptoms of systemic anaphylaxis due to the protamine components of NPH insulin in whom tolerance to protamine and to NPH insulin was induced by hyposensitisation.

A 16-year-old diabetic patient was seen for the first time at the diabetes clinic of the Central University Hospital, Caracas, in February, 1981. Diabetes had been diagnosed at age 4 years. Daily subcutaneous NPH insulin of bovine origin was prescribed. After two years of continuous therapy, the patient presented generalised urticaria and facial angio-oedema about 5 min after the injection. The medication was suspended. Every time he received NPH insulin, the symptoms recurred. Regular and lente insulin of bovine origin were tried: there were no allergic manifestations but metabolic control was not satisfactory.

To try and identify the cause of the reactions intradermal provocation tests were done. Saline and regular insulin (80 units/ml, Eli Lilly) gave negative reactions but both protamine sulphate (Sigma) and NPH insulin yielded ++++ reactions (wheal with pseudopoda).

Hyposensitisation with protamine sulphate was achieved with a series of fifteen subcutaneous injections in the arm, 20 min apart, in a single session. The dose was increased, 0.1 mg at a time, from 0.1 to 1.5 mg. Local reactions ceased after the 0.7 mg injection. At the end of the session 5 units of NPH insulin was injected subcutaneously. Neither local nor systemic symptoms of anaphylaxis occurred.

The patient now takes insulin NPH 45 units in the morning and 20 units in the afternoon, supplemented with 20 units of regular insulin. His blood glucose is stable at 80–150 mg/dl, and 95% of urine tests are negative for sugar. No symptoms of allergy due to insulin have appeared, and the intradermal test with NPH insulin remains negative after 9 months of observation.

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WHICH INSULIN FOR DIABETIC KETOSIS?

SIR,—In replying to the assertion that "only purified porcine insulin should be used to treat diabetic ketosis" (March 27, p. 737), Dr McDermott and Dr Cullen (May 15, p. 1129) suggest that purified bovine insulin might prove to be a suitable alternative in newly diagnosed diabetics. We feel that this ignores the evidence that both species and purity are important in the immunogenicity of an insulin preparation. Bovine insulin in conventional, "purified", or "single component" form, is inherently more immunogenic than porcine insulin,^{2,3} eliciting higher levels of IgG antibodies, which

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4. Dougherty RJ. Pseudo-speed look-alike or pea shooters. *NY State J Med* 1982; **1**: 74–75.

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