TABLE III—Principal features of adverse reactions associated with thiopentone (estimated administrations 86 000)

No	Age (years)	Sex	Reaction	Operation	Medical details	Other details
1	16	F	Histaminoid: Bronchospasm; cyanosis; cardiac arrest; facial oedema	Appendicectomy		Also given atropine, suxamethonium. Allergic to adhesive plaster
2	28	F	Bronchospasm; hypotension; cardiac arrest	Tubal ligation		Also given suxamethonium, pancuronium. Allergic to penicillin
3	21	F	Bullous skin lesion; hypotension	Dilatation and curettage		
4	67	M	Miscellaneous: Cyanosis; hypotension; cardiac arrest	Cystoscopy	Ischaemic heart disease	
5	78	M	Cyanosis; hypotension; cardiac arrest	Ureterotomy	Ischaemic heart disease	Also given pancuronium
6	?	F	Rigidity of jaw muscles; laryngospasm; cyanosis	Dilatation and curettage	Obese, heavy smoker	

rigidity with apnoea or airway obstruction managed by muscular paralysis and endotracheal intubation. Two patients developed apnoea of ten and 30 minutes' duration.

Reactions associated with thiopentone—Three histaminoid reactions were reported which led to cardiac arrest in two patients (table III). Both of these patients had a history of allergy, one to penicillin and the other to adhesive strapping, and each received other drugs—atropine and suxamethonium (case 1), and suxamethonium and pancuronium (case 2). In another two patients, cardiac arrest preceded by hypotension was reported; both were elderly, aged 67 and 78 respectively, with ischaemic heart disease and impaired renal function. These reactions were believed to have resulted from a relative overdose of thiopentone.

Incidence of reactions—The overall incidence of adverse reactions associated with Althesin was one in 930 (95% confidence limits: one in 650 to one in 1650), and with thiopentone one in 14 000 (95% confidence limits: one in 6600 to one in 39 300). The incidence of histaminoid reactions to Althesin was one in 1900 and thiopentone one in 29 000. The incidence of other adverse reactions after Althesin was one in 1900 and one in 29 000 for thiopentone.

Discussion

We found that the incidence of adverse reactions to Althesin was fifteen times greater than that to thiopentone. Previous estimates of the incidence of adverse reactions to Althesin have varied. Clarke *et al* correlated a series of spontaneous reported adverse reactions (including those submitted to the Committee on Safety of Medicines) with the national sales of Althesin, and estimated the overall incidence to be one in 11 000.² Watt³ and Fisher⁴ both reported four histaminoid reactions in 3500 administrations (one in 900).

A predominance of female patients as in this series was also found in the series reported by Clarke *et al*.² The selective use of Althesin in short gynaecological procedures and preponderance of women patients requiring anaesthesia in our series (about 60%) may account for this bias. The incidence of reactions would have been higher if any of the 22 anaesthetists who did not reply to questionnaires had reported adverse reactions.

The reactions associated with Althesin reported in this study were similar to those previously reported, except for the two cases of apnoea. Short periods of apnoea may be produced by a relative overdose of intravenous anaesthetic agent; in neither case did we consider this a satisfactory explanation. The four reports of convulsions after Althesin in fit patients raises the question of its safety in patients with a predisposition to convulsions. Enhancement of epileptiform electroencephalographic changes after Althesin have been observed in patients with pre-existing intracranial disease and previously detected electroencephalographic changes.⁵ The incidence of neuromuscular reactions to Althesin is influenced by the rate of injection and choice of premedication.^{6,7} Although Althesin was not injected rapidly in the three cases of severe muscle rigidity, the use of hyoscine for premedication in two cases may have contributed to the severity of the reactions.

Serious adverse reactions to thiopentone have been considered uncommon, only 30 cases having been reported.¹ The reactions associated with thiopentone reported to us were notable only for their rarity. Possibly the true incidence of adverse reactions is greater. Retrospective collection of reports of adverse reactions to long-established agents is likely to be incomplete. The collection of reactions associated with a new agent such as Althesin, however, is likely to be more reliable.

Two factors may explain the substantial discrepancy between our estimates of the incidence of adverse reactions to Althesin and those made by Clarke *et al*.² Firstly, our definition of an adverse reaction probably encouraged the reporting of reactions other than histaminoid reactions. Secondly, the collection of reports by questionnaire and interview is certain to be more productive than spontaneous reporting. Only nine of the 26 reactions collected by us were published or

reported to the Committee on Safety of Medicines. The deficiency of spontaneous reporting as a method of assessing adverse reactions is well recognised, and has become a matter of public concern.⁸ Proposals to overcome this by a system of monitored or controlled release have recently been discussed.⁹ New anaesthetic agents could be subject to monitored release with relative ease since their administration is performed and closely supervised by anaesthetists. Most important reactions to a new induction agent, for example, could be shown by monitoring 10 000–20 000 administrations.

The relative safety of Althesin as an induction agent must again be questioned.^{3,4,10} Although Althesin has the advantages over thiopentone of causing little postanaesthetic sedation and little irritation when given extravascularly or intra-arterially, we believe the high incidence of adverse reactions (approximately one in 1000 administrations) increases the risks of anaesthesia to a generally unacceptable level.

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Generalised allergic reaction to monocomponent insulin

Generalised allergic reactions to insulin were recognised soon after its introduction into medicine.¹ Both a delayed-type hypersensitivity and an immediate-type hypersensitivity to insulin have been described.^{2,3} These reactions are, however, extremely rare and they have not been reported with the monocomponent insulins. We describe here a patient who developed a generalised allergic reaction to a monocomponent insulin.

Case report

A 23-year-old female diabetic developed a local weal to soluble insulin when it was given for a short period in 1965. The insulin was stopped and she

was treated with oral hypoglycaemic agents until 1976, when she presented with symptoms due to deteriorating diabetic control. Isophane insulin was started but she developed a local weal four hours after her second injection. Despite changing first to LeoRetard and then Actrapid MC this problem became worse and she developed weals up to 40 mm in diameter at her injection sites. Seven weeks after her initial injection, while still on Actrapid MC, she had several episodes of generalised urticaria associated with angioneurotic oedema. Withdrawal of insulin alleviated her signs and symptoms within 48 hours. Challenged with 6 units of Actrapid MC subcutaneously she sweated transiently at 10 minutes and developed generalised urticaria at four hours, which lasted for 12 hours.

There was a strong family history of allergy and the patient herself described allergies to penicillin, salmon, and trout. Intradermal tests were performed with 2 units each of Actrapid MC, Semitard MC, LeoRetard, Nuso Neutral Insulin (pure beef insulin), and soluble and isophane insulin, and 0.1 ml of Actrapid transport medium, methylparaben (a constituent of the transport medium), and physiological saline. All the insulin sites showed a weal at four hours that lasted for 12 hours, while the transport media produced no reaction. All the tests, including those with transport media, but apart from the control showed a transient erythema at 10 minutes.

After the Actrapid MC challenge the neutrophil count rose transiently at 30 minutes from $6.3 \cdot 10^9/l$ to $11.5 \cdot 10^9/l$. There was no change up to 18 hours in C3, C4, C3 conversion, or total IgE concentrations or blood eosinophil count.

Insulin antibodies were present and the IgG binding capacity for bovine insulin was $6.8 \mu g/\mu l$ (upper normal limit $10 \mu g/\mu l$) with an avidity of $0.1 \text{ litres mol} \cdot 10^9$ (upper normal limit for a person receiving heterologous insulin $0.5 \text{ litres mol} \cdot 10^9$). After desensitisation the antibody binding capacity increased to $19.5 \mu g/\mu l$ and the avidity was $2.3 \text{ litres mol} \cdot 10^9$.

She was successfully desensitised to Actrapid MC, though it took four weeks to achieve. Four subcutaneous injections were given daily starting with 0.001 units of Actrapid MC and increasing the dose slowly as previously described.² To obtain a therapeutic dose of 10 units per injection without a local weal developing 2 mg hydrocortisone was added to each insulin injection.

Comment

This generalised urticarial reaction to porcine monocomponent insulin resembled a delayed-type hypersensitivity reaction, though there was a mild immediate reaction to the insulins and the transport media. The increase in the IgG insulin antibody after successful desensitisation suggested that it was not implicated in this reaction, because its concentration would otherwise have decreased. Desensitisation is essential since subsequent exposure to insulin might be disastrous.⁴ This rare complication still occurs despite the introduction of the monocomponent insulin.

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Pressor response after intravenous labetalol

Labetalol (Trandate) is a new hypotensive agent with both alpha- and beta-blocking properties. The intravenous preparation is recommended for treating hypertensive crises both as initial therapy¹ and in patients already receiving beta-adrenergic blocking drugs.²

We describe here a patient on hypotensive treatment in whom intravenous labetalol produced a pressor response.

Case report

A 19-year-old Caucasian man presented with nephrotic syndrome in 1973. This was shown to be due to a type I membranoproliferative glomerulonephritis and C3 nephritic factor was present. Haemodialysis was begun in November 1976 and he received a cadaveric renal transplant in February 1977. The graft functioned successfully but he developed severe hypertension. Transplant renal artery stenosis was excluded. Bilateral nephrectomy was performed in April 1977 leaving the graft kidney in situ. After operation the blood pressure fell and rose again. Diastolic pressures of 130-140 mm Hg were found despite treatment with methyldopa 0.75 g, propranolol 960 mg, guanethidine 75 mg, Moduretic two tablets, prednisolone 30 mg, and azathioprine 200 mg daily.

On readmission he weighed 65.9 kg, the fundi showed arteriovenous nicking, and the blood pressure was 165/120 mm Hg lying and 185/130 mm Hg standing. The creatinine clearance was 57 ml/minute, the plasma renin 15 060 pg/ml of plasma/hour (grossly raised), and plasma aldosterone 4502 pmol/l (162 ng/100 ml) (normal $< 330 \text{ pmol/l}$ (12.0 ng/100 ml)). His existing treatment was continued and the patient was also given three separate intravenous bolus doses of labetalol, as shown in the figure, two of which produced a further increase in the blood pressure.

Comment

The increase in blood pressure after intravenous labetalol was probably related to the drug. It occurred twice and the pressor response was not considered to be the result of anxiety because intravenous hydralazine produced a prompt and sustained fall in blood pressure (see figure).

Increase in blood pressure after 0.75 mg/kg (50 mg) and 0.38 mg/kg (25 mg) of intravenous labetalol. All measurements were made in the lying position and the diastolic end point was taken at the 4th Korotkoff phase.

Hypertension can be induced in normotensive subjects by propranolol in rapid oral incremental doses,³ and augmentation of hypertension has been observed when the dose of sotalol is increased too rapidly.⁴ Presumably these pressor effects are related to an increase in total peripheral resistance, which is a feature of many of the beta-adrenergic blocking drugs. The beta-blocking component of labetalol probably added to that already present from propranolol and thus exacerbated the hypertension in our patient. We are unaware of any reports of blood pressure changes after intravenous labetalol in patients already receiving methyldopa or guanethidine.

We suggest that bolus intravenous labetalol should be given with caution to patients who are already taking substantial doses of beta-blockers, methyldopa, or guanethidine until the interaction has been clarified, since a severe pressor response could be fatal.

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