Furthermore, in man a correlation was observed between the disappearance rate of ^{125}I -insulin and changes in blood glucose values both at rest^{5, 6} and during exercise.⁴ Thus these data show that measuring the fall in radioactivity at the site of insulin injection by external counting reflects the insulin disappearance rate and suggest that the absorbed insulin is biologically active.

In my study sauna accelerated the absorption of insulin from the subcutaneous injection site in the leg. While in the sauna the disappearance rate of insulin from subcutaneous tissue was two-fold greater than during the same period on the control day (fig 2). As to the mechanism of the sauna-induced rise in insulin absorption, studies show that local heating increases subcutaneous blood flow and accelerates insulin absorption from the injection site, whereas local cooling decreases the insulin disappearance rate.¹² Although I did not measure skin temperature or blood flow, the augmented insulin delivery during the sauna may be explained at least partly by enhanced blood flow at the subcutaneous injection site. Interestingly local degradation of insulin may occur at the subcutaneous injection site.^{5, 13} Thus sauna by augmenting insulin absorption may decrease the local degradation of injected insulin, thus further increasing biological activity of insulin.

Of particular interest was the effect of the sauna on blood glucose concentrations. After the sauna the postprandial rise in glucose values was less and the values fell to lower levels than on the control day (fig 3). My observations may have clinical implications for the management of insulin-treated diabetics, particularly those who take a sauna soon after insulin injection. Since a large depot of injected insulin may remain at the injection site the stimulatory effect of the sauna on insulin absorption may result in a rapid fall in blood glucose. Thus in such patients a snack or small reduction in insulin dose (or both) may prevent hypoglycaemia after a sauna.

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SHORT REPORTS

Pulmonary fat embolism treated by intermittent continuous positive airway pressure given by face mask

Fat embolism is a serious complication in patients with severe injury and a fractured bone.¹ The main symptoms are fever, dyspnoea and tachypnoea, restlessness, and confusion. Clinical signs are a petechial rash, radiographic evidence of diffuse alveolar infiltrates in both lungs, hypoxaemia, and lipuria. Treatment consists in giving oxygen, mechanical ventilation, and corticosteroids.² We report on a patient treated by intermittent continuous positive airway pressure given via a face mask by the patient himself.^{3, 4}

Case report

A 25-year-old healthy man was admitted to hospital with a fracture of the shaft of his left femur caused by falling from a horse. The fracture was treated by continuous traction. After 39 hours he developed headache, his temperature rose to 38°C and pulse rate to 104/min, and he complained of chest pain and nausea. He was slightly dyspnoeic and had a petechial rash on his chest and abdomen. Chest radiographs were normal, his arterial oxygen pressure (PaO_2) was 6.3 kPa (47.3 mm Hg; normal range 10-14 kPa (75-105 mm Hg)), and his arterial carbon dioxide pressure (PaCO_2) was normal. Treatment was started with oxygen 5 l/min via a nasal catheter. Fractional inspired oxygen (FIO_2) cannot be calculated in this method but was probably in the range of 0.4-0.5. Heparin 10 000 units intravenously and dexamethasone 4 mg were given every six hours and dextran 500 ml infused every 12 hours. Twenty-four hours later his condition was unchanged. Radiographs now showed diffuse infiltrates of both lung fields, PaO_2 was 6.0 kPa (45 mm Hg), PaCO_2 4.8 kPa (36 mm Hg), and FIO_2 0.4-0.5.

At this stage we considered intubation and continuous mechanical ventilation plus positive end expiratory pressure, but we favoured intermittent continuous positive airway pressure since the patient had no cerebral symptoms, could co-operate, and could operate the apparatus himself. Continuous positive airway pressure was given for five minutes every half hour during the daytime and for five minutes every hour during the night. At a pressure of 100 mm H_2O (0.1 kPa) oxygen 7 l plus atmospheric air 7 l was given via a nebuliser (FIO_2 0.6). The earlier treatment was continued unchanged, including oxygen by nasal catheter, except that the oxygen flow was increased from 5 l/min to 7 l/min and the nasal catheter was taken out when continuous positive airway pressure was given. After five hours PaO_2 rose to 11.4 kPa (85.5 mm Hg), but PaCO_2 was unchanged, as were the x-ray pictures. After two days the chest radiographs were normal. After four days oxygen treatment could be stopped and continuous positive airway pressure was given without extra oxygen (FIO_2 0.21). After seven days all treatment was stopped, and 12 days after the injury (10 days after starting continuous positive airway pressure) fixation of the fracture was carried out without complications.

Comment

Continuous mechanical ventilation with positive end expiratory pressure is well known and widely accepted, having been used since 1969 in treating acute respiratory insufficiency. Its efficacy in reducing pulmonary venous admixture and improving arterial oxygenation seems to be related to increasing functional capacity when terminal closure and atelectasis are present.⁵ The same effect can be achieved by continuous positive airway pressure, which is useful in patients who can maintain spontaneous breathing. Positive end expiratory pressure and continuous positive airway pressure are similar in effect, but the former is used in connection with mechanical ventilation and the latter with spontaneous respiration. Continuous positive airway

pressure is tiring and can be given only periodically. It offers a useful alternative to continuous mechanical ventilation plus positive end expiratory pressure when treatment is prolonged and the patient can breathe spontaneously.⁴ There are few reports on the use of continuous positive airway pressure in adults, but our case shows that it may be an alternative to continuous mechanical ventilation plus positive end expiratory pressure in treating the adult respiratory distress syndrome.

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Interference of a propranolol metabolite with serum bilirubin estimation in chronic renal failure

Some patients with chronic renal failure have shown consistently raised serum bilirubin concentrations, as measured by an automated diazo technique (SMA 12/60, Technicon Instruments). Hyperbilirubinaemia, however, was not detected with the Bilirubinometer (British American Optical Company), which uses a direct photometric technique rather than a chemical reaction. Since all of these patients had been given antihypertensive agents, we have investigated the possibility that this interference with the diazo reaction (which we have called "false bilirubin") was due to retention of a drug in chronic renal failure.

Subjects, methods, and results

We obtained a list from the department of chemical pathology of all patients in the five months from 20 March 1979 with raised serum bilirubin concentrations (over 14 $\mu\text{mol/l}$ (0.84 mg/100 ml), diazo technique), normal liver function values (serum aspartate aminotransferase activity under 40 IU/l and alkaline phosphatase activity under 130 IU/l), and serum creatinine concentrations over 400 $\mu\text{mol/l}$ (4.5 mg/100 ml). There were 21 such patients (table). All were suffering from chronic renal failure, and all but three were taking propranolol.

Stored, frozen sera obtained from 13 of the 21 patients, including two of the three patients not receiving propranolol, were retested using a diazo technique,¹ and by the Bilirubinometer. All but one of the sera from patients taking propranolol showed abnormal diazo reactions and normal Bilirubinometer results, indicating the presence of "false bilirubin." The samples from the two patients who were not taking propranolol showed raised bilirubin concentrations when tested with both the Bilirubinometer and the diazo reaction. They therefore had true hyperbilirubinaemia. Thus all the patients with "false bilirubin" were taking propranolol.

We used 15 consecutive patients with chronic renal failure who were neither undergoing dialysis nor receiving propranolol as control subjects. Study of the case notes of these patients showed that they had never had hyperbilirubinaemia (diazo technique, data available from authors on request). The report by Andrewes² of false-positive diazo reactions in uraemic sera almost certainly referred to patients who were more uraemic and had a more active catabolism than ours.

Serial studies on several patients receiving a constant dose of propranolol showed that there was a relation between the "false bilirubin" concentration and the serum creatinine concentration. When haemodialysis was started the "false bilirubin" values fell, despite the continued administration of propranolol. Peritoneal dialysis did not seem as effective in removing this substance.

The table shows that 13 of the 21 patients were taking hydralazine. We found, however, that neither hydralazine itself nor eight known metabolites interfered with the diazo reaction. We also found that propranolol itself did not interfere with the diazo reaction, but that two of its metabolites, 4-hydroxypropranolol and 1-naphthol, gave false-positive results. 4-Hydroxypropranolol is a major hepatic metabolite of propranolol and is excreted in the urine as glucuronide and sulphate conjugates.³

Several serum samples from our patients were treated with glucuronidase and sulphatase, which deconjugate these compounds, and were examined by two-dimensional thin-layer chromatography. This showed that the substance in these sera that reacted with the diazo reagent had, after deconjugation, identical chromatographic properties to 4-hydroxypropranolol.

Propranolol dose and serum bilirubin and creatinine concentrations in 21 uraemic patients with apparent hyperbilirubinaemia

Case	Propranolol (mg/day)	Bilirubin ($\mu\text{mol/l}$)		Creatinine ($\mu\text{mol/l}$)
		Diazo technique	Bilirubinometer	
1*	0	21		730
2*	0	34	30	615
3†	0	48	40	960
4*	1280	25		465
5*	640	15		595
6	480	25		1565
7	1280	23		545
8	160	18		525
9	360	18	< 10	605
10*	1280	51	< 10	1030
11	1280	74		1105
12*‡	1280	33	< 10	655
13*	640	19	< 10	560
14*	640	36		675
15*†	640	33	< 10	1285
16*	1280	22	15	440
17*	1280	39	> 10	950
18†	640	15	> 10	760
19*	320	23	> 10	1255
20‡	1280	57	> 10	465
21*§	1280	60	20	680

*Patient taking hydralazine.

†Patient underwent peritoneal dialysis.

‡Patient underwent haemodialysis.

§Lipaeic serum.

Conversion: SI to traditional units—Serum bilirubin: 1 $\mu\text{mol/l}$ $\approx$ 0.06 mg/100 ml. Serum creatinine: 1 $\mu\text{mol/l}$ $\approx$ 0.01 mg/100 ml.

Comment

We have shown that a propranolol metabolite, a conjugate of 4-hydroxypropranolol that is normally excreted in the urine, accumulates in the plasma of undialysed patients with chronic renal failure and interferes with the widely used diazo reaction to give falsely raised bilirubin concentrations, which may cause confusion clinically and lead to unnecessary investigations. The Bilirubinometer, available in most neonatal units, provides a simple way of avoiding this source of error.

We thank Dr A J Pinching for encouraging us to undertake this study and discussing it with us, the department of chemical pathology for permission to use their results, and Professor D K Peters for allowing us to study patients under his care.

Addendum

Since this study was completed a report⁴ has appeared of a similar phenomenon, proposing that the false hyperbilirubinaemia is due to an unidentified metabolite of propranolol.

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