Metabolic Responses to Beta₂ Stimulants

S. ROLF SMITH, MD, MRCP(UK), Senior Registrar
M.J. KENDALL, MD, FRCP, Senior Lecturer
Department of Therapeutics and Clinical Pharmacology, Queen Elizabeth Hospital, Edgbaston, Birmingham

The advent of the beta₂ stimulants such as salbutamol and terbutaline has made a major impact on the treatment of patients with asthma and bronchitis. These selective agents may be given in relatively small doses directly into the bronchial tree by the use of aerosol inhalers and this has increased their efficiency and reduced their adverse effects. For those who are unable to learn the technique of aerosol use there are now modifications such as the addition of a spacer chamber which avoids the need to coordinate inspiration with aerosol delivery, and the oral route remains an alternative option. For the treatment of the acute severe exacerbation of asthma, high doses of these agents may be given by inhalation using a nebuliser face mask, or smaller doses may be given intravenously. Another major use of these drugs is in the treatment of premature uterine contractions during pregnancy.

On the whole, these agents are well tolerated but, in common with most other groups of drugs, they can produce unwanted responses. These tend to occur when large doses are used and are the predictable effects of stimulating beta receptors at sites other than the bronchial tree. These responses can be divided into three main groups: (a) tremor; (b) cardiovascular responses, including tachycardia and a rise in systolic blood pressure, and (c) the metabolic responses that are the subject of this review. This diversity of unwanted responses reflects the wide distribution of beta₂ receptors throughout tissues which include striated muscle, vascular smooth muscle, liver and pancreas. Of the metabolic responses, the effects on potassium, carbohydrate and lipid metabolism are the best documented.

Potassium

Mechanism

The involvement of beta receptors, specifically beta₂ receptors, in potassium homeostasis is well documented and many studies on the effects of infusion of adrenaline have been performed. In the 1930s D’Silva[1] showed that serum potassium concentrations fell in cats when adrenaline was injected and subsequent studies of pancreactectomised and nephrectomised animals have shown this to be independent of insulin, aldosterone and renal elimination of potassium[2]. In vitro studies using isolated rat or guinea-pig soleus muscle have shown that isoprena-line, salbutamol, adrenaline and noradrenaline all stimulate 42K-uptake and increase the amount of intracellular potassium[3,4,5,6]. These actions could be abolished by ouabain, which shows that they were the consequence of increased sodium-potassium transport. That these changes were due to stimulation of the beta₂ adrenergic receptors is indicated by in vitro and in vivo studies. Using the rat soleus muscle Clausen and Flatman[5] showed that the adrenaline-induced increase in resting membrane potential 31Na-efflux and ouabain-suppressible 42K-uptake were completely blocked by propranolol, whereas the beta₂ agonist salbutamol was at least a hundred times as potent as a beta₂ agonist in stimulating sodium efflux and potassium influx[5]. These results suggest that this hypokalaemic response is mediated via beta₂ receptors linked to membrane sodium-potassium ATPase causing potassium influx.

Studies in man using adrenergic challenge under different conditions of beta blockade have supported the contention that the receptor involved is a beta₂ adrenoceptor. In one study in which adrenaline was infused intravenously into normal volunteers, the fall in serum potassium was completely prevented by the non-selective adrenoceptor blocker timolol, but only partially reduced by the selective beta blocker, atenolol[7]. In another study, adrenaline-associated hypokalaemia was abolished by a selective beta₂ antagonist (ICI 11851) and independent of the release of renin, aldosterone and insulin[8]. In a third, propranolol had a greater effect than metoprolol on terbutaline-induced hypokalaemia[9].

Potassium Response to Beta₂ Agonists in Clinical Practice

The in vitro and in vivo evidence indicating the association between stimulation of beta₂ adrenoceptors and a fall in serum potassium has been put to therapeutic use. For example, patients with hyperkalaemic familial periodic paralysis have been treated with inhalation of salbutamol. This alleviated hyperkalaemia and paralysis precipitated by exercise or oral administration of potassium chloride[10]. It is possible, however, that therapeutic doses of beta₂ agonists used in the treatment of asthma or premature labour may cause significant hypokalaemia that might be hazardous under certain conditions. The potass-
ium response to beta₂ agonists administered in a variety of ways has been assessed in normal volunteers, patients with airflow limitation and pregnant women undergoing therapy for premature uterine contractions.

In normal young volunteers, using a slow (one hour) infusion of a dose of terbutaline commonly used in clinical practice (0.5 mg), the serum potassium fell by almost 0.9 mmol/litre[11]. This hypokalaemic response was the same in young and old people; the haemodynamic reactions differ according to the age of the subject[12]. Other beta₂ agonists, including salbutamol and rimiterol, given intravenously in therapeutic doses produce significant falls in serum potassium, which range from 0.4 mmol/litre to 1.2 mmol/litre[13,14]. When salbutamol was given by aerosol in a dose of 200 μg (two puffs), no change in serum potassium was observed[15] but nebulisers deliver much higher doses, which may induce significant changes. In a recent study, 5 and 10 mg of salbutamol, which are conventional doses in nebuliser therapy, were given over an eight minute period to nine healthy volunteers and changes in serum potassium occurring during the subsequent hour were monitored. The mean maximum fall in the serum potassium was 0.36 mmol/litre after 5 mg[16]. Presumably the blood levels of salbutamol necessary to produce this response were achieved by absorption of drug from the respiratory tract and, probably to a greater extent, from the gastrointestinal tract, since quite a large proportion of the dose delivered is trapped in the pharynx and swallowed. The hypokalaemic response to beta₂ agonists is not peculiar to the healthy volunteer but is also shown in studies on asthmatics. Patients with chronic asthma and those with acute attacks treated with intravenous salbutamol show significant falls in the level of serum potassium[15,17]. Four micrograms per kilogram given over 10 minutes produced a mean fall of 0.45 mmol/litre and similar changes were observed after the same treatment had been given during the following few days[17].

Several papers have also reported significant falls in the potassium level following treatment of patients in premature labour with either intravenous or subcutaneous salbutamol[18-20]. The urinary excretion of potassium remains unchanged[20], which supports the experimental work already discussed showing that the hypokalaemia following beta₂ stimulation is due to a shift of potassium into the cells and not due to loss in the urine.

Clinical Significance of Hypokalaemic Response

A fall in serum potassium is a reproducible consequence of treatment with beta₂ stimulants. The magnitude of the fall is sufficient to produce hypokalaemia, especially if the pre-treatment level of potassium was low. The important question is whether this degree of hypokalaemia is of any clinical relevance. This is a difficult question since the importance of hypokalaemia, diuretic-induced hypokalaemia particularly, has been a matter for debate. There is evidence to suggest that hypokalaemia predisposes to ventricular arrhythmias[21,22] and that diuretic-induced hypokalaemia is associated with increased ventricular ectopic activity[23]. It might be argued that this is due to a reduction of the total body potassium and a concomitant depletion of intracellular stores of potassium, which is in contrast to the situation that follows treatment with beta₂ agonists, when there is a shift of potassium into the cells. However, after long-term diuretic therapy, there does not seem to be any marked influence on total body potassium[24] nor does diuretic-induced hypokalaemia lead to a fall in intracellular potassium content[25]. It seems that it is the fall in the extracellular rather than the intracellular potassium concentration that is important in determining the risk of cardiac arrhythmias. Also following myocardial infarction, patients with low or low normal serum potassium levels appear to be at greater risk from serious ventricular arrhythmias[21,26-28]. It is possible that the fall in potassium in this situation is a paraphenomenon and that other factors such as a rise in circulating adrenaline may be responsible for both the arrhythmia and the fall in serum potassium. On balance, it seems that hypokalaemia is best avoided.

Some of the clinical situations in which treatment with a beta₂ agonist is indicated are those in which serum potassium may already be low or low normal. For example, patients with exacerbations of chronic airways obstruction are commonly treated with these agents, often using a nebuliser, and many of these will have co-existing ischaemic heart disease for which they may be taking diuretics, possibly with digoxin. In this situation a further reduction in potassium may increase the risk of cardiac arrhythmias to which patients with hypokalaemia taking maintenance digoxin therapy are exposed[29]. Long-term treatment of chronic airways disease with corticosteroids may also lower serum potassium. Since there is a potential risk, which is easily avoided, clinicians should be aware of the problem and should include an early serum potassium estimation on those patients who are to be given beta₂ stimulants, particularly if they could already be hypokalaemic. This should obviously not delay treatment of the very acute attack.

Other Electrolytes

Changes in serum magnesium, calcium and phosphate have also been reported to occur in response to beta₂ stimulation. Using slow infusions of beta₂ agonists, a significant fall in serum calcium and magnesium levels and dose-related decreases in plasma phosphate have been demonstrated[14]. The mechanisms responsible for these changes are unclear but may in part be due to the rise in the circulating insulin level that occurs in response to beta₂ stimulants, as discussed below. At the moment the risks associated with these changes are only theoretical.

Glucose and Insulin

Beta₂ receptors are also involved in glycogenolysis and insulin release. Glycogen breakdown in skeletal muscle can be precipitated by stimulation of beta₂ receptors[30,31]. Although glycogenolysis is believed to be operated by an alpha-adrenergic mechanism in the liver, beta receptors may also play a role[32].
Elevations in circulating glucose levels in response to treatment with beta_2 agonists have been reported widely in the literature. Using varying therapeutic doses of intravenous terbutaline, salbutamol or ritodrine in normal volunteers, different authors have demonstrated quite marked increases in plasma glucose levels. For example, when 1 mg of terbutaline was infused over 60 minutes in one volunteer, the glucose level rose by almost 5 mmol/litre above basal levels[11], and an infusion of 0.7 μg/kg/min of salbutamol for 90 minutes produced a maximum rise of more than 6 mmol/litre[14]. Similarly, when given to women in late pregnancy, intravenous, subcutaneous and oral terbutaline and salbutamol have been shown to produce hyperglycaemia. After parenteral administration, hyperlactacidaemia also occurred[19,20,33]. With regard to the inhaled route of administration, even two puffs (200 μg) of aerosol salbutamol given to patients with mild chronic asthma produced a small, transient but statistically significant rise in plasma glucose of 0.2 mmol/litre after two minutes[15]. After 5 mg of nebulised salbutamol, given to nine normal volunteers, the mean maximum rise in plasma glucose was 0.7 mmol/litre[16].

Catecholamines have also been shown to stimulate insulin release via the beta_2 receptor. The rise in insulin levels in man following isoprenaline (a non-selective beta receptor stimulant) is blocked totally by the non-selective beta-adrenergic blocker propranolol, but only partially by the selective beta-blocker metoprolol[32]. It might be argued that the hypokalaemic response to beta_2 stimulation could be secondary to the associated rise in insulin levels. Although this may be a contributory factor, it would seem to be relatively minor since adrenaline, a potent beta agonist, also causes hypokalaemia but has an inhibitory effect on insulin release[34]. Elevations of serum insulin have been documented following intravenous infusion of salbutamol into normal volunteers[13,14,35], into patients with chronic asthma[15], and after the administration of intravenous and subcutaneous terbutaline to pregnant women[19,20]. Even a single oral dose of 4 mg of salbutamol produces a significant sustained rise in the plasma level of insulin in normal volunteers[36], and a rise in C-peptide in pregnant women[33].

The question arises whether there are any situations in which these changes in glucose and insulin levels following treatment with beta_2 agonists assume clinical significance. It seems probable that the simultaneous rise in insulin serves to attenuate the rise in plasma glucose. As might be anticipated, the rise in glucose levels is more marked in diabetic patients given beta_2 agonists. Intravenous salbutamol has been shown to produce significantly greater elevations of glucose and ketone body concentrations in diabetic than in non-diabetic patients[37,38]. Hyperglycaemia ketoadidas can also be reported to occur in previously well-controlled diabetic women following treatment of premature labour with intravenous salbutamol[39]. It would seem advisable, therefore, to use these agents with caution in diabetics, and to monitor plasma glucose levels closely in order to prevent the occurrence of hyperglycaemia.

**Lipids**

Catecholamines play an important role in the degradation of stored triglyceride to fatty acids and glycerol. Although the beta_2 adrenergic receptor is thought to be mainly responsible for catecholamine-stimulated lipolysis, beta_2 agonists also exhibit some lipolytic activity[40]. The involvement of the beta_2 receptor in lipolysis is supported by the finding that the adrenaline-induced rise in free fatty acids is significantly smaller following pre-treatment with the non-selective beta-blocking drug, pindolol, than it is following the beta_2 selective drug, atenolol[41]. A number of studies have shown that conventional doses of beta_2 stimulants produce significant changes in the products of lipolysis. For example, a single 4 mg dose of oral salbutamol given to healthy men caused a significant rise in plasma free fatty acid levels after 60 minutes[36], and the same dose given to a group of pregnant women produced a significant rise in the level of glycerol after 90 minutes[33]. Similar changes have been observed in response to the intravenous administration of salbutamol in normal subjects[35] and in asthmatics during both an acute attack and the recovery phase[17]. These changes are exaggerated in diabetes, intravenous salbutamol causing a greater rise in free fatty acid, glycerol and ketone body concentrations than in normal subjects[37,38].

Changes in other lipid fractions have also been reported to occur in response to beta_2 stimulation. Hooper et al.[42] showed that when a group of normal subjects was given oral terbutaline 2.5 mg four times daily for a two week period, there was a significant elevation of HDL-cholesterol concentration, which returned to baseline values one week after terbutaline administration was stopped. Total cholesterol, LDL-cholesterol and triglyceride levels did not change significantly throughout the study. These results are of particular interest in view of the association between high levels of HDL-cholesterol and a reduced risk of coronary artery disease.

**Tolerance**

The preceding discussion relates to the metabolic responses to acute beta_2 stimulation. Treatment with the oral and inhaled preparations of these agents, however, may be prolonged and it is important to know whether these metabolic responses are sustained for weeks and months or not. For some responses there is evidence to suggest that prolonged administration may cause tolerance (i.e. desensitisation or tachyphylaxis) to develop. However, data on this subject are not so consistent as those from the acute studies. Some parameters may be more affected than others and healthy volunteers may differ from patients.

*In vitro* studies have shown that polymorphonuclear cells from asthmatic and healthy volunteers have fewer beta receptors after treatment with oral terbutaline than do the cells of untreated patients or controls, indicating that treatment with adrenergic agonists can down-regulate beta adrenergic receptors[43]. This change in receptor numbers seems to correspond to changes in cardiovascular responses to beta-adrenergic stimulation,
suggested that down-regulation in peripheral blood cells may reflect similar changes in other tissues[44].

Results of some in vivo studies in man support the concept of down-regulation of beta receptors after long-term exposure to beta agonists, and normal volunteers, pregnant women and asthmatic patients have been investigated. In one report normal subjects were challenged daily for two weeks with intravenous salbutamol administered before and after the administration of 1,600 μg of inhaled salbutamol. Whereas the initial infusion produced the typical changes described above, as well as a dose-dependent increase in specific airways conductance, after long-term inhalation of salbutamol there was a decrease in the airways and metabolic responses to intravenous salbutamol, with attenuation of the rise in glucose, insulin, lactate, glycerol, free fatty acids and ketone bodies[45]. Using a similar technique, the same group has shown that in mild asthmatics, some of the metabolic responses, including the rise in blood glucose and pyruvate, were similarly depressed after regularly inhaled salbutamol. However, in contrast to normal volunteers, no impairment of the insulin, lactate, free fatty acid, glycerol or ketone responses was demonstrated in asthmatics. In addition, after four weeks of treatment with inhaled salbutamol the therapeutic airway response to intravenous salbutamol was still demonstrable, which suggests that asthmatic subjects are protected to some extent from developing resistance[46,47]. Thus there seems to be variation in the case with which tissues develop resistance to beta-adrenoceptor agonists, the glucose response tending to be affected more readily than the glycerol and free fatty acid responses[48]. This concept is supported by the results of other studies. For example, a group of pregnant women who had received regular oral salbutamol (4 mg four times daily) for at least 12 days, showed a significantly less pronounced rise in glucose, insulin and lactate levels following a 4 mg oral dose of salbutamol than those who had not been exposed to a beta-adrenoceptor agonist before. However, there were significant increases in the levels of free fatty acids and 3-hydroxybutyrate in both groups and although there was a tendency for the responses to be greater in the group that had not been previously treated with beta-stimulants, the differences were not significant[49].

The development of tolerance also applies to apply to the hypokalaemic response to beta2 stimulants, at least in normal volunteers. In one study, in which oral terbutaline 5 mg three times daily for 13 days was used, the fall in serum potassium shown to occur after oral dosing on day 1 was no longer demonstrable on day 13[50].

Conclusion

From the discussion above it can be seen that the unwanted metabolic responses to therapeutic doses of beta, stimulants are wide ranging, and reflect the generalised distribution of beta2 receptors throughout the tissues. Under certain circumstances the responses following short-term administration of relatively high doses may be particularly undesirable, examples being the hypokalaemic response in patients with chronic bronchitis and underlying ischaemic heart disease, and the glycolgenolytic and lipolytic responses in diabetics. In the majority of cases, however, these responses probably do not present a significant risk to the patient and some of them diminish with prolonged treatment. Nevertheless, the clinician who has to interpret laboratory data needs to be aware of the possible effects of these drugs, particularly if the patient is a diabetic.

References

1. D’Silva, J. L. (1934) Journal of Physiology, 82, 393.
2. Lundberg, P. (1983) Acta Medica Scandinavica, Suppl., 672, p.121.
3. Clausen, T. and Flatman, J. A. (1977) Journal of Physiology, 270, 383.
4. Flatman, J. A. and Clausen, T. (1979) Nature, 281, 380.
5. Clausen, T. and Flatman, J. A. (1980) British Journal of Pharmacology, 68, 749.
6. Buur, T., Clausen, T., Holmberg, E., Johansson, U. and Waldock, B. (1982) British Journal of Pharmacology, 76, 313.
7. Struthers, A. D., Reid, J. L., Whitesmith, R. and Rodger, J. C. (1983) Clinical Science, 65, 143.
8. Brown, M. J., Brown, D. C. and Murphy, M. B. (1983) Clinical Science, 64, 71P (Abstract).
9. Smith, S. R., Kendall, M. J., Worthington, D. J. and Holder, R. (1983) British Journal of Clinical Pharmacology, 16, 557.
10. Wang, P. and Clausen, T. (1976) Lancet, 1, 221.
11. Kendall, M. J., Dean, S., Bradley, D., Gibson, R. and Worthington, D. J. (1982) Journal of Clinical and Hospital Pharmacy, 7, 31.
12. Kendall, M. J., Woods, K. L., Wilkins, M. R. and Worthington, D. J. (1982) British Journal of Clinical Pharmacology, 14, 821.
13. Eich, A. G., Clancy, L. J., Costello, J. F. and Fenley, D. C. (1976) British Medical Journal, 1, 365.
14. Phillips, P. J., Vedig, A. B., Jones, P. L. et al. (1980) British Journal of Clinical Pharmacology, 9, 483.
15. Neville, A., Palmer, J. B. D., Gaddie, J., May, C. S., Palmer, K. N. V. and Murchison, L. E. (1977) British Medical Journal, 1, 413.
16. Smith, S. R., Kendall, M. J. and Ryder, C. (1984) Clinical Science, 66, 40P. (Abstract).
17. Nogrady, S. G., Hartley, J. P. R. and Seaton, A. (1977) Thorax, 32, 559.
18. Smith, S. K. and Thompson, D. (1977) British Journal of Obstetrics and Gynaecology, 84, 344.
19. Smythe, A. R. and Sakakini, J. (1981) Obstetrics and Gynaecology, 57, 566.
20. Cotton, D. B., Strassner, H. T., Lipson, L. G. and Goldstein, D. A. (1981) American Journal of Obstetrics and Gynaecology, 141, 617.
21. Cole, A. G., Arkin, D. and Solomon, R. J. (1981) In International Congress and Symposium Series No. 44, p.9. (ed C. Wood and W. Somerville, London: Royal Society of Medicine.
22. Thomas, R. and Hicks, S. (1981) Clinical Science, 60, 32P. (Abstract).
23. Holland, D. B., Nixon, J. V. and Kuhntert, L.v. (1981) American Journal of Medicine, 70, 762.
24. Elmloftt, D., Berglund, G., Wedel, H. and Wilhelmson, L. (1983) Acta Medica Scandinavica, Suppl. 672, p.79.
25. Poole-Wilson, P. A. (1981) In International Congress and Symposium Series No. 44, p.9. (ed C. Wood and W. Somerville, London: Royal Society of Medicine.
26. Nordeheug, J. E. (1981) Acta Medica Scandinavica, Suppl. 647, p.109.
27. Hulting, J. (1981) Acta Medica Scandinavica, Suppl. 647, p.109.
28. Thomas, R. D. (1983) Postgraduate Medical Journal, 59, 354.
29. Steiness, E. and Olesen, K. H. (1976) British Heart Journal, 38, 167.
30. Stoll, J. T. and Mayer, S. E. (1971) Journal of Biological Chemistry, 246, 5716.
31. Gross, S. R. and Mayer, S. E. (1974) Life Sciences, 14, 401.
32. William-Oldson, T., Fellenius, E., Bjortorp, P. and Smith, U. (1979) Acta Medica Scandinavica, 205, 201.
33. Lunell, N. O., Wager, J., Fredholm, B. B. and Persson, B. (1978) European Journal of Clinical Pharmacology, 14, 95.
Book Review

Advanced Medicine Leeds, edited by M. S. Losowsky and R. P. Bolton. Pitman Books Ltd, London, 1983. Price £27.50.

This book contains short papers based on presentations given at the College Advanced Medicine Conference held in Leeds in 1982. There are 34 contributions from writers who are, in the main, of international repute. Their brief was to aim at the non-specialist general physician, and to review new trends, to improve the standard of practice of the non-expert, or to critically assess a field of study.

I attended the Leeds Conference and, as a general physician, found the proceedings often exciting and stimulating, almost always of interest, and only occasionally stupefyingly boring. The papers in the book are based very closely on the presentations, but there are few illustrations, and no discussion has been included. There is little evidence of editorial control, and the papers vary greatly in style and length. However, the references are well presented and are right up to date, including some 1983 papers. The index is easy to use, and is efficient.

While the book is divided into sections, each paper stands by itself, and there is no cross reference. The content covers a wide area. There is a strong emphasis on clinical pharmacology, with ten papers on different groups of drugs. These do not cover new ground for the practising physician, although they would be useful for those studying for examinations. Their value lay in the opportunity for the discussion of practical points in therapeutics.

More profitable papers discuss the management of common problems (ischaemic heart disease, self-poisoning, neurosis), and of less frequently seen disorders (vasculitis, adult respiratory distress syndrome, Paget’s Disease). A section entitled Infections from Unusual Angles includes adult cystic fibrosis, opportunistic infections, and antibiotic-associated diarrhoea. This type of review, with up to date references, saves the busy physician valuable time.

Other contributors explain for the beginner such complex subjects as monoclonal antibodies, nuclear magnetic resonance, bone marrow transplantation, and the continuing saga of the hepatitis B virus. These papers will help the struggling postgraduate of any age to keep his end up in the MCQ or after-dinner conversation.

The paper which I enjoyed the most, and which deserves a much wider audience, was ‘The Common Problem of Non-Disease’. The author, a dermatologist, discusses the mysteries of non-classifiable non-organic symptoms, and reviews the recent literature on the subject. His thoughts on the medical profession’s response to this challenge, and the iatrogenic disease generated as a consequence, are well worth reading.

Is this a useful book for the postgraduate working for examinations, and for the physician anxious to keep up to date? The answer must be yes, so far as any book can be a medium for the interchange of ideas. It will certainly be of value to the Membership candidate for Part I as well as Part II, and should be in the postgraduate library. It is more difficult to recommend the impoverished physician to pay £27.50 for a personal copy. I found the book hard to read through because of the frequent changes in topic and style and the occasional inadequate paper. However, when used as a reference book, for short dips as need arises, I think it will prove valuable, and should remain so for some years.

ALISON ROSS