UNCERTAINTIES PAGE

Should antihistamines be used to treat anaphylaxis?

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Anaphylaxis is a serious allergic reaction that is rapid in onset and potentially fatal.[1] Guidelines and experts agree that adrenaline (epinephrine) is the first line treatment for anaphylaxis.[2] Internationally, however, treatment guidelines differ widely,[3]and the widespread use of antihistamines in anaphylaxis, often as first line treatment instead of adrenaline, has led to concern.[4 5]

What is the evidence of uncertainty?

International guidelines are conflicting on the use of antihistamines in anaphylaxis

No randomised controlled clinical trials or observational studies exist to inform us: a Cochrane review recently failed to identify any randomised controlled clinical trials evaluating antihistamines in acute anaphylaxis[6]; only one prospective trial was identified but was excluded as it lacked a control group and did not study patients with anaphylaxis.[7] Our own PubMed search also did not identify any randomised controlled clinical trials or observational or cohort studies examining the appropriateness of antihistamines in anaphylaxis.

Unsurprisingly, a recent comparison of important international guidelines found conflicting advice about antihistamines,[3] reflecting the uncertainty in international clinical practice: a US guideline recommends the use of diphenhydramine as second line treatment in anaphylaxis[8]; evidence for this recommendation is graded as "expert opinion/extrapolated from higher order evidence."[9] An Australian guideline advises against the use of antihistamines in anaphylaxis (except in special circumstances).[10] The Resuscitation Council of the United Kingdom still recommends chlorphenamine as second line treatment after initial resuscitation, grading evidence to support its use as weak but citing some physiological reasons for its use (refuted below).[11]Admittedly a recent Cochrane review also found no prospective controlled trials on the benefits of adrenaline in anaphylaxis eligible for inclusion.[12] However, the review's authors, as with all other guidelines, recommend adrenaline as first line treatment for anaphylaxis, based on expert consensus and indirect observational data.

Antihistamines are too little, too late and potentially detrimental

Antihistamines are widely recommended in anaphylaxis for their anti-allergenic properties, which comprise the inhibition of mediator release from mast cells and basophils.[13] However, firstly, antihistamines have no proved clinical effect on the immediate and life threatening symptoms of anaphylaxis. In conventional doses, antihistamines fail to prevent the massive release of histamine observed in anaphylaxis.[6] They are slower in onset than adrenaline and have little effect on blood pressure. They play a negligible role in relieving bronchospasm or gastrointestinal symptoms, relegating them to second tier treatment.[1 13] As a consequence they may just be useful for relief of mild symptoms, such as allergic reactions limited to the skin or the mucous membranes and flushing, itching, urticaria, and rhinorrhoea.[14] Treatment with both H1-antagonists (antihistamines) and H2-antagonists (such as cimetidine and ranitidine) combined is more effective in alleviating the cutaneous manifestations of anaphylaxis than H1-antagonists alone.[15 16]

Secondly, especially in susceptible patients (genetic predisposition, drug overdose, electrolyte imbalance, those taking certain medications, or those with coronary artery disease), the risk of potentially fatal cardiac arrhythmias such as QT prolongation and torsade de pointes argues against the administration of older, first generation intravenous H1 antihistamines.[17 18] The anticholinergic properties of these older drugs may lead to tachycardia and sedation, potentially confusing the picture in anaphylaxis. Newer, less toxic third generation antihistamines are unfortunately only available orally. In fasting adults, these have a delayed onset of 40-60 minutes, greatly reducing their utility in acute anaphylaxis.[15]

Thirdly, a logistical problem of delay exists. In serious cases, the earlier the adrenaline is injected, the more effective it is,[1 11 19] but the great interpersonal variability makes the need for early adrenaline administration unforeseeable and unpredictable.[16] An inexperienced physician or lay person might delay the livesaving adrenaline injection, favouring a presumed innocuous (but ineffective) antihistamine.[9]

If antihistamines are ineffective in serious cases, with a slow onset, and potentially detrimental, and if they may even delay the lifesaving adrenaline injection, should we still use them in anaphylaxis? To avoid any hesitation by the first responder, treatment algorithms should be straightforward: "First and foremost, give adrenaline . . ."[16]

This is a series of occasional articles that highlights areas of practice where management lacks convincing supporting evidence. The series advisers are David Tovey, editor in chief, the *Cochrane Library*, and Charles Young, editor of *BMJ Clinical Evidence* and editor in chief, *BMJ Point of Care*."

Is ongoing research likely to provide relevant evidence?

An inquiry of various experts and an examination of several registers of clinical trials found no ongoing randomised controlled clinical trials on antihistamines in anaphylaxis. A recent review outlined some particular ethical and logistical challenges that randomised controlled clinical trials on anaphylaxis may pose, such as the difficulty with informed consent and randomisation for out of hospital trials.[20] Clinical presentation of anaphylaxis shows a high variability, indicating the need for large numbers in a trial. Will ethical review boards accept a placebo controlled trial while antihistamines are recommended in several international guidelines? With uncertain outcome, pharmaceutical sponsoring is unlikely. Randomised controlled clinical trials in emergency medicine, however, have been successfully completed—for example, on vasopressin in cardiac arrest. Indeed, a randomised controlled clinical trial on anaphylaxis with a suitable design is under way but is not evaluating whether antihistamines should be used to treat anaphylaxis (trial NCT00657228, clinicaltrials.gov). The box outlines recommendations for further research.

What should we do in the light of the uncertainty?

Keep it simple; inject adrenaline first. In anaphylaxis, universal consensus is to give adrenaline intramuscularly. International guidelines recommend 0.01 mg/kg and/or a maximum of 0.3-0.5 mg for adults.[3] Antihistamines should never be given alone or instead of adrenaline in anaphylaxis.[8] First do no harm: because of possible adverse effects and until randomised controlled trials prove a beneficial effect, antihistamines should be considered only after adrenaline administration and with caution. They may be indicated, if at all, mainly to relieve itching, hives, other cutaneous symptoms, and rhinorrhoea. We suggest that clinical guidelines emphasise the need for avoidance or caution and the absence of evidence supporting their use. We strongly support the need for pertinent randomised controlled trials.

RECOMMENDATIONS FOR FURTHER RESEARCH

Population: Adult and/or paediatric patients with anaphylaxis. Patients in need of snake antivenom might be an ideal population because of the high incidence of anaphylaxis occurring under controlled conditions

Intervention and comparison: Randomised controlled trial of oral or intravenous antihistamines compared with placebo

Outcome: Whether the antihistamines result in reduced mortality. Secondary outcomes should include delays in the administration of adrenaline or a reduction in the need for further doses of adrenaline, adverse effects of antihistamines, and morbidity outcomes such as cardiovascular instability

METHODS

We combined a free text search with a controlled vocabulary search in PubMed and trial registries (Controlled-trials.com and ClinicalTrials.gov), from the inception of the databases to May 2009. From 253 hits in PubMed and 358 in the trial registries we did not identify any completed or ongoing randomised controlled trials on antihistamines in anaphylaxis

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A PATIENT'S JOURNEY

Living with a benign brain tumour

Anne McDonald

After surgical removal of a benign brain tumour, Dr Anne McDonald suffered residual neurological defects that led to her retirement. She has found the symptoms and their effects difficult to come to terms with

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"You have a tumour in the fourth ventricle." Shock. Sudden scrabbling in the memory for anything I learnt at medical school about neuroanatomy—that was over 30 years ago! I realised two things: first, the doctor was doing his utmost not to call it a brain tumour, and, second, he was watching me with trepidation to see if I would burst into tears. "I will refer you urgently to the neurosurgeons."

From my symptoms I had already self diagnosed an acoustic neuroma, and had little idea about the implications of this new diagnosis, except that it was a brain tumour! My immediate thoughts were of the last patient I had looked after with a similar diagnosis. He was dead within six months; it had been like an immediate death sentence. So how long did I have? Would I see either of my sons graduate? What would my husband do? This crystallisation of priorities increased my determination to stay alive.

Unsurprisingly, nobody was prepared to give my husband and me any predictions for the future, and I was told exactly what I had been expecting—that it was impossible to make an accurate diagnosis without tissue samples. I was given the choice of urgent neurosurgery or waiting for six months to see if the tumour grew. Would I be alive in six months' time to make a decision? I felt that I had no option but to go ahead with the surgery. The only potential complications I remember being discussed openly were dementia and incontinence. As the doctor saw the look of frozen horror on my face, our discussion ceased. Perhaps I should have asked more.

Consequences of a benign brain tumour

Two months later, in March 2005, the tumour was removed, and I was fortunate to have survived a difficult operation and its complications, thanks to the competence of the neurosurgeon and his team. It was a benign subependymoma, and I have residual neurological defects necessitating medical retirement. I have found both the symptoms and their effects very difficult to come to terms with, and retrospect always brings more questions.

The intensive care unit and the high dependency unit were both distressing and lonely places to be. I have memories of both, even though the medication I took means I'm not supposed to be able to. It was frustrating to be paralysed in the dark, but able to hear people around me discussing me in the third person rather than addressing me directly. My musical abilities had not gone, so I could identify the speaker by the "music" of their voice, which was very upsetting if they wanted to "write me off"! I would have valued anyone coming and talking to me as a normal human being, even if my body was apparently on its last legs.

Continuous positive airway pressure is extremely unpleasant and seemed, if anything, to make it more difficult to breathe. I was not compliant with it, and the disintegration of the apparatus was partly my fault—nobody suspected that I was "with it" enough to have figured out both how the apparatus worked and how to sabotage it! Perhaps the design could be modified?

At times I was very distressed because much of the experience felt so humiliating. I was actively discouraged from crying, although it might have proved helpful.

Even now, my memories of hospital are painful.

I didn't see the consultant neurosurgeon who operated on me until after his return from holiday, by which time I had become an outpatient. During my hospital stay, junior members of staff had repeatedly mentioned the possibility of radiotherapy, which implied to me malignancy or, at the very least, secondary tumours. The internet was not helpful in clarifying my situation and prospects, and my husband banned me from looking up my diagnosis because he thought it would cause too much distress.

I spent the weeks before the appointment with my consultant in a haze of anxiety, sorting out finances, papers, and wills. However, on my outpatient visit, the consultant removed the threat of radiotherapy. The effect of being categorically told that no further treatment was needed was indescribable!

After my consultant emigrated, my care was transferred to his successor, who reviews me with magnetic resonance imaging.

Support

It would have been helpful to have been given details of a local support group. The only one I have been able to find is Headway (www.headway.org.uk). Unfortunately their regular meeting was on the only night of the week that my GP husband was guaranteed to be home from work, and we decided not to get involved. I now feel that this was a mistake, but we were both in shock and struggling to cope. A care package had not been organised, and we were very much on our own. I have trawled the internet for any other relevant organisation, but drawn a blank. Perhaps readers can help?

This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

A DOCTOR'S PERSPECTIVE

"Your friend and colleague has a tumour in the fourth ventricle." Shock.

One's immediate reaction to such information is not unlike that experienced by those directly affected, and Anne herself notes the behaviour of the doctor breaking her bad news. True, he may have wanted to avoid using the phrase "brain tumour" and might have been anxious in case Anne broke down, but he too would have been surprised, upset, and worried by the discovery. Paternalism also probably intervened, and he may have attempted to minimise the gravity of the diagnosis for her. He might have feared tears on her part, as these could have represented the breakdown of a partly professional relationship, something that at that point both Anne and her doctor perhaps perceived as enabling them both to cope with this difficult information.

Anne writes movingly of her concerns for her family first and foremost. One realises that doctor or not, her needs and wishes are identical to those of every other patient. The message is that colleagues encountered in this setting should be treated as patients and not professionals. The time to rebuild your professional relationship will come later, in times of good health. The attempt to preserve a professional association may also mean less open discussion, a failure to admit lack of knowledge or experience, and the absence of firm direction on treatment. You are simply too careful about what you say. I have often noted an "inverse care law"—where medical professionals and their relatives have suffered because of assumptions made about their level of knowledge or their capacity to secure services. Anne's (eventually successful) search for therapy services in the community is a good illustration.

Some of Anne's many clinical observations postoperatively are difficult to account for, for example, the persistent fatigue and sensory overload. They are nevertheless real and must be related to her tumour and the surgery she underwent. The ignorance and callousness of the pensions company is not unexpected (note the plaudits for the BMA!) but do we not dismiss the claims of other patients with identical symptoms in the absence of demonstrable pathology as being manufactured? Perhaps terms such as "non-organic" and "functional" should be stripped of their negative connotations, and interpreted as "we simply do not know"?

This insightful and thought provoking account is a salutary reminder that treating one's colleagues is a privilege and an honour, and that their needs are surprisingly ordinary. If they seek you out, they probably do so because they consider you a good and kind doctor, and not because you are an opinion leader, a brilliant academic, or a management wizard.

There has been no map for my journey, and I have had no companions. I was given little idea of what to expect, and am usually told, even at my specialist outpatient clinics, that "we don't have many patients like you." Perhaps I should have insisted on being referred to a major centre where I could have met patients with similar problems, whose experiences, I believe, might have offered a great deal. The internet has been helpful for looking up the neuroanatomy involved (for example at www.netterimages.com). No doctor has been able to explain to me my rather complicated neurology, perhaps because of lack of time. But I find the need to know why my physical state is as it is compelling nevertheless. With a little time, and three dimensional mental imaging, it has been possible for me to form an understanding of my condition—but what of the patients who are not able to do this because of lack of knowledge or ability?

Community physiotherapy was of paramount importance, although I had to be persistent to get it. It was very hard work, but it gave me direction, focus, and, vitally, hope. The positive attitude, knowledge, and encouragement of the physiotherapists were instrumental in my achieving major improvements in the first year after surgery. I had to be motivated, however, or physiotherapy would have been a waste of resources.

There was an administrative mix up about community occupational therapy, which meant I was not seen at home for about nine months. I didn't chase because I didn't know I'd been referred! The aids, once obtained, were very useful, though.

I would not be where I am today without the major support of family and friends. They have, when necessary, also been critical of my lack of awareness of my physical state and needs, which has been hard to take at the time, but usually correct.

I also have a physiotherapist friend who is continuing to treat me, without whose experienced input I would not have the abilities I have today, and to whom I remain indebted.

My GP has been most helpful, mainly for providing prescriptions and filling in the innumerable paperwork necessitated by my changing roles and lifestyles. She and I have remained in contact throughout my treatment, and I have known that she is there if I ever need her.

I have seen a psychologist for debilitating flashbacks to my time in hospital, which are triggered by unexpected things—as, for example, when I was sitting in a totally different hospital's cafe and became aware of the smell of the wards coming through the heating system. Getting into the system required dogged persistence on my part, but it was certainly worth it. I believe that patients who have brain surgery are now routinely seen by a psychologist during their hospital stay, and I hope this will make such problems less likely to arise.

Coping and what is needed along the way

My symptoms vary daily. Tiredness and poor sleep are definitely deleterious, as are stress and overstimulation. There is a "brick wall" point where I am forced to stop. It feels like a mental "traffic jam" where making decisions, thinking at all, and even talking may be impossible. I find that the only answer is rest, with me lying flat to stop as much excess sensory input to the brain as possible, especially from the head and neck muscles, for at least 30 minutes. I then become aware of the traffic jam clearing, which is a great relief.

My sympathetic nervous system has also been affected, so I now drink decaffeinated tea and coffee to reduce palpitations. Even a splash of wine is enough to cause effects, which my family find hilarious, but which I prefer to avoid. Central coldness (very different from just feeling cold) is unpleasant,

but I can cope with it by having a hot drink and as hot a bath as I can tolerate, and by getting into bed with a thick dressing gown on under the duvet until it passes, again usually after 30 minutes or so. Flushes require the opposite. There can be a demarcation line across the body between the two, both occurring at the same time.

Progress has been painfully slow, but it has been made, and it is very easy to forget how far I have come. I found making very specific lists helpful. I list what I can do now and couldn't do six months ago. It is depressing to list what I can't do now, unless my physiotherapist and I are focusing on an achievable goal—how, for example, to get out of the back door to put something in the dustbin without falling over! Functional, small, achievable. I rapidly learnt that I couldn't metaphorically jump straight to the top of the stairs, but had to take them one at a time.

Being a doctor, my life had been full of what I "ought" to be doing. I have had to change my thinking radically into "doing what I am able", and just "being" rather than achieving. When depressed, I try to think of six things I am grateful for every day, which I find surprisingly easy.

Losing the path

One of the most stressful incidents was having my request for medical retirement turned down by the NHS Pensions Agency, which meant I then had to appeal. I felt I was being accused of lying about my medical state and found this very hurtful; I felt disbelieved and as if I were being called a fraud. The BMA's pensions department was superbly helpful, though, as was the support of a local consultant. I have two lever arch files of official communications, and without my husband's help (I have problems with my sight), and that of those above, I would have completely lost the plot. It was a very distressing time.

I understand now why those who have been very ill often become housebound, even if their physical state suggests they could do more. The familiar causes no anxiety, and it takes a definite act of will deliberately to put oneself into unknown situations. Fear is difficult to overcome. I found it easiest to try to do small things incrementally: to go to the front gate, then to the corner of the road, then to the post box and on to visit an understanding friend, all done regularly until they cause no further anxiety and they too become familiar.

Journey's end

I have been told that the tumour was benign, but I have lost confidence in my body and am glad to have been offered follow-up magnetic resonance imaging scans. I live with the enduring fear that the tumour will return, whatever logic might suggest to the contrary. Whether my symptoms will improve, nobody will hazard a guess. For all of us the very end will be death, and I am aware I have already journeyed to its gates. Whether that means death will come to me sooner rather than later, I have no idea. But I regard this experience as a second chance, a challenge to live life now, and try to enjoy it as much as possible, for however long I have.

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Consulting with veiled students

After 35 years in general practice, I have been contracted to teach family medicine at a national university medical school in the Middle East. I thought that changing from clinical practice to full time teaching would be easier, but teaching practice and theory have undergone a sea change since I was at medical school in the 1960s.

On top of this have been the challenges of teaching in a completely different culture where the male and female students are taught separately. This involves my lecturing directly to the men while a camera and microphone relay my image and voice to another part of the medical school where the women are sitting.

The same occurs in the clinics, where the students come separated into female and male groups and about a third of the female students wear veils (niqabs). A few even come wearing long black gloves. As most of the female patients are also veiled and I don't understand Arabic it is sometimes difficult to assess and mark a consultation between a veiled medical student and a veiled patient. We are researching ways of doing this based on our experience of how consultations are normally conducted, as well as the use of non-verbal communication, paralinguistics, and intuition. The feedback from the student is, thankfully, in English, which backs up our assessments.

A problem I didn't anticipate occurred while I was examining in an OSCE history exam. The simulated patient was an elderly British man, and it was his first time as a simulated patient. The first female student was not wearing a veil and asked the patient how he was, and they had a merry old conversation. The second student, who was veiled, came in and asked him his name and there was a complete silence. She then asked him about his symptoms. Again complete silence. I then asked him if he had heard the student, to which he replied that he was about 70% deaf and relied mostly on lip reading.

I informed all the following veiled students that they should shout the questions. The proctor in the corridor outside inquired afterwards as to why my students were so angry with the patient.

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Patient consent not required (patient anonymised, dead, or hypothetical).

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10-MINUTE CONSULTATION

Thyroid swellings

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A 48 year old post-menopausal woman presents with a smooth midline swelling in her neck, which has been present for more than 10 years. On examination, you find that it is consistent with an enlarged thyroid gland.

What issues you should cover

- A palpable thyroid swelling (defined as a goitre) may be physiological if the patient is pregnant or going through puberty.
- Patients who have lived in an iodine deficient area (for example, north Pakistan, central Africa, and mountainous areas such as the Andes or Himalayas) are at increased risk of goitre.
- Lithium, amiodarone, and antithyroid drugs (such as carbimazole and propylthiouracil) can predispose to goitre.
- Thyroid swellings are more likely to be malignant in patients over 65 years or in women during their reproductive years.
- Common differentials for swellings in the central component of the neck include thyroglossal cysts (which move on tongue protrusion), dermoid cysts (easily moved under the skin), lipomas, and sebaceous cysts.
- Risk of malignancy is similar for both solitary and multiple nodules. The size of the nodule does not determine malignant potential. A hard, fixed nodule is, however, more indicative of malignancy.
- A tender swelling may be a sign of subacute (viral) thyroiditis.

What you should do

Examination

- Inspect the fully extended neck in good lighting to accentuate any masses. Palpate the neck appropriately to determine the nature of the swelling.
- Ask the patient to swallow—if the swelling is from the thyroid gland, it and any nodules will move; swellings outside the thyroid gland will not.
- Ask about symptoms of hyperthyroidism or hypothyroidism. Most swellings are not associated with thyroid hormone dysfunction.
- Exclude malignancy in nodular swellings. Ask about compressive symptoms such as dysphonia, dysphagia, and dyspnoea (the three Ds), all of which are suggestive of malignancy.
- Ask how long the patient has had the swelling. Most benign swellings grow insidiously over many years. A swelling or nodule that enlarges over weeks or months is suggestive of malignancy.
- Ask about relevant family and previous medical history. Patients with a history of head and neck irradiation, a family history of thyroid cancer, or familial adenomatous polyposis have an increased risk of malignancy.
- Palpate for cervical lymphadenopathy, which implies possible metastatic spread.
- Auscultate the thyroid for bruits, which may be present in Graves' disease.
- Elicit Pemberton's sign if you suspect a retrosternal goitre (for example, if compressive symptoms are present): ask the patient to raise both arms simultaneously above the head and see whether the face becomes plethoric. This is a sign of venous obstruction as a result of retrosternal goitre extension.

Management

- Refer immediately to a specialist any patient with a high risk of malignancy because of previous thyroid cancer, family history of thyroid cancer, compressive symptoms, or lymphadenopathy.
- For patients not at risk of malignancy, perform thyroid function tests, including those that measure concentrations of serum thyroid stimulating hormone and free levothyroxine, to uncover any thyroid hormone dysfunction.
- Arrange a follow-up appointment to discuss the thyroid function test results. Reassure the patient that swellings associated with hyperthyroidism are nearly always benign and can be referred to an endocrinologist.
- Refer patients with nodular thyroid swelling and normal thyroid function test results to a specialist thyroid clinic for thyroid ultrasound and possible fine needle aspiration.

This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs

USEFUL READING

For professionals

American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi. Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocrine Practice* 2006;12:63-102
Hegedus L. Clinical practice: the thyroid nodule. *N Engl J Med* 2004;351:1764-71
Polyzos SA, Kita M, Avramidis A. Thyroid nodules—stepwise diagnosis and management. *Hormones* 2007;6:101-19
National Institute for Health and Clinical Excellence covers management of thyroid cancer in their head and neck cancer guidelines (www.nice.org.uk). The updated guidelines for thyroid cancer from the Royal College of Physicians are available on their website (www.rcp.ac.uk)

For patients

American Thyroid Association (www.thyroid.org)
British Thyroid Association (www.british-thyroid-association.org)
Cancer research UK (www.cancerhelp.org.uk)

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DRUG POINTS

Rimonabant may induce atrial fibrillation

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Rimonabant is a selective cannabinoid-1 receptor blocker that has been shown to reduce weight and improve several cardiovascular risk factors in obese patients.[1-5] In a review article, although the frequent occurrence of psychiatric adverse events was mentioned, rimonabant was still recommended in the treatment of overweight patients with type 2 diabetes and metabolic syndrome in whom lifestyle changes are not sufficiently effective.[6 7] The drug was recently withdrawn by the European Medicines Agency (www.nice.org.uk/TA144), but it is likely to remain available over the counter and through the internet. We report two cases of atrial fibrillation in overweight patients treated with 20 mg/day rimonabant.

Case description

Case 1

During the first two weeks of therapy the patient reported mild nausea and insomnia; after four weeks he had lost 1.9 kg; and after five weeks he reported palpitations, fatigue, and exertional dyspnoea. Examination was unremarkable apart from atrial fibrillation with ventricular rate between 98 and 135 beats/min. Thyroid function tests and electrolyte serum values were normal. Serum glucose was slightly increased and the concentration of free fatty acids was high (42.8 g/100 g). A stress echocardiogram showed a mild, concentric left ventricular hypertrophy; however, the regional contraction and global contraction of the left ventricle were normal. Pulmonary pressure was normal. Anticoagulation was started with phenprocoumon and low molecular weight heparin until the international normalised ratio was ≥2, and then continued with phenprocoumon alone. Rimonabant was stopped, and amiodarone was started. Two weeks later the electrocardiogram showed that atrial fibrillation had reverted to sinus rhythm. The patient refused a re-challenge with rimonabant. After 9 months atrial fibrillation had not recurred.

Case 2

During the first week of therapy with rimonabant the patient reported nausea; after three weeks he had lost 1.7 kg, but at the same time he reported dizziness, palpitations, and exertional dyspnoea. Examination was unremarkable apart from atrial fibrillation. Thyroid function tests, serum glucose, and electrolytes were normal. However, the concentration of free fatty acids had increased from 17.8 g/100 g before treatment to 38.9 g/100 g. A stress echocardiogram detected a mild, concentric left ventricular hypertrophy and a minimal mitral regurgitation; however, the regional motility and the global function of the left ventricle were normal. The pulmonary pressure was also normal. Atorvastatin and metformin were left unchanged. Because of possible interactions, rimonabant was stopped, and metoprolol was replaced with amiodarone. Anticoagulation was started with phenprocoumon and low molecular weight heparin until the international normalised ratio was ≥2, and then continued with phenprocoumon alone. Ten days later the electrocardiogram showed that atrial fibrillation had reverted to sinus rhythm with a first degree atrioventricular block. Amiodarone was replaced with metoprolol. Two weeks later in an electrocardiogram control, sinus rhythm persisted and the atrioventricular block had disappeared. The patient and his family physician attributed the atrial fibrillation to rimonabant treatment.

Conclusion

Cardiovascular side effects of non-cardioactive drugs are common and often unpredictable; atrial fibrillation is a rare but potentially dangerous side effect.[8] The effect of rimonabant on the cardiovascular system is almost unknown, but was presumed to be beneficial because of its effects on body weight and metabolism of glucose and lipids.[1-6 9] However, the results of the STRADIVARIUS study[10] show that in patients with abdominal obesity and coronary artery disease, rimonabant was associated with an almost 50% risk of psychiatric side effects, a threefold increased risk of gastrointestinal side effects, and a tripling in the risk of erectile dysfunction, but did not improve the progression of atherosclerosis.

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